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=> s osteoporosis and calcilyt? and maphthyl and ethyl and amine
L2 0 OSTEOPOROSIS AND CALCILYT? AND MAPHTHYL AND ETHYL AND AMINE

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L3 157 OSTEOPOROSIS AND CALCILYT?

=> s l1 and naphthyl and ethyl and amine
L4 0 L1 AND NAPHTHYL AND ETHYL AND AMINE

=> s l3 and naphthyl and ethyl and amine
L5 26 L3 AND NAPHTHYL AND ETHYL AND AMINE

=> d 15 1-26 ab

L5 ANSWER 1 OF 26 IFIPAT COPYRIGHT 2003 IFI on STN
AB The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
receptor activity. Also described are the use of **calcilytic**
compounds to inhibit calcium receptor activity and/or achieve a
beneficial effect in a patient; and techniques which can be used to
obtain additional **calcilytic** compounds.

L5 ANSWER 2 OF 26 USPATFULL on STN
AB Novel **calcilytic** compounds and methods of using them are
provided.

L5 ANSWER 3 OF 26 USPATFULL on STN
AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl,
bis(arylmethyl)amino, bis(heteroarylmethyl)amino and
arylmethyl(heteroarylmethyl) amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl,
sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8
and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

L5 ANSWER 4 OF 26 USPATFULL on STN
AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

L5 ANSWER 5 OF 26 USPATFULL on STN

AB The present invention features **calcilytic** compounds. " **Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

L5 ANSWER 6 OF 26 USPATFULL on STN

AB Novel **calcilytic** compounds and methods of using them are provided.

L5 ANSWER 7 OF 26 USPATFULL on STN

AB The present invention features **calcilytic** compounds. " **calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

L5 ANSWER 8 OF 26 USPATFULL on STN

AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl) amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

L5 ANSWER 9 OF 26 USPATFULL on STN

AB The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

L5 ANSWER 10 OF 26 USPATFULL on STN

AB Novel **calcilytic** compounds are provided.

L5 ANSWER 11 OF 26 USPATFULL on STN

AB Novel **calcilytic** compounds, pharmaceuticals compositions containing said compounds and their use as calcium receptor antagonists.

L5 ANSWER 12 OF 26 USPATFULL on STN

AB **Calcilytic** compounds and compositions and their use in treating abnormal bone or mineral homeostasis.

L5 ANSWER 13 OF 26 USPATFULL on STN

AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.P--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

L5 ANSWER 14 OF 26 USPATFULL on STN

AB Novel **calcilytic** compounds are provided.

L5 ANSWER 15 OF 26 USPATFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sup.2+ and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

L5 ANSWER 16 OF 26 USPTAFULL on STN

AB Novel arylalkylamino compounds exhibiting calcilytic properties are provided.

L5 ANSWER 17 OF 26 USPTAFULL on STN

AB A compound selected from Formula (I) hereinbelow: ##STR1##

or a pharmaceutically acceptable salt thereof, wherein

m is an integer from 0 to 2; n is an integer from 1 to 3;

X is selected from the group consisting of CN, NO.sub.2, Cl, F, and H;

Y is selected from the group consisting of Cl, F, Br, I and H; and

Q and Z are, independently, selected from the group consisting of H, R.sub.1, SO.sub.2 R.sub.1 ', R.sub.1 C(O)OR.sub.1 ", SO.sub.2 NR.sub.1 'R.sub.1 ", C(O)NR.sub.1 'R.sub.1 ", NR.sub.1 'SO.sub.2 R".sub.1, wherein R1, R.sub.1 ' and R.sub.1 " are independently selected from the group consisting of hydrogen, C.sub.1-4 alkyl, C.sub.3-6 cycloalkyl, C.sub.2-5 alkenyl, C.sub.2-5 alkynyl, heterocycloalkyl, aryl and aryl C.sub.1-4 alkyl; or R.sub.1 ' and R.sub.1 " together form a 3 to 7 membered optionally substituted heterocyclic ring; wherein any substituents are selected from the group consisting of CN, aryl, CO.sub.2 R, CO.sub.2 NHR, OH, OR, NH.sub.2, halo, CF.sub.3, OCF.sub.3 and NO.sub.2 ; wherein R represents H, C.sub.1-4 alkyl, and C.sub.3-6 cycloalkyl; and A is phenyl or naphthyl, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6 cycloalkyl, OSO.sub.2 R.sub.1, CN, NO.sub.2, OCF.sub.3, CF.sub.3, and CH.sub.2 CF.sub.3, (CH.sub.2).sub.n CO.sub.2 H, (CH.sub.2).sub.n CO.sub.2 R.sub.1, and O--(CH.sub.2).sub.n CO.sub.2 R.sub.1, wherein n is an integer from 0 to 3 0-3 and R.sub.1 represents C.sub.1-4 alkyl, C.sub.3-6 cycloalkyl, C.sub.3-6 cycloalkyl, heteroaryl or fused heteroaryl (wherein the hetero-ring can contain N, O or S and can be aromatic, dihydro or tetrahydro) unsubstituted or substituted with any substituents being selected from the group consisting of OH, OCH.sub.3, CH(CH.sub.3).sub.2, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6 cycloalkyl, CN, NO.sub.2, OCF.sub.3, CF.sub.3, CH.sub.2 CF.sub.3, (CH.sub.2).sub.n CO.sub.2 R.sub.1, and O--(CH.sub.2).sub.n CO.sub.2 R.sub.1 is provided.

L5 ANSWER 18 OF 26 USPTAFULL on STN

AB The present invention features compounds able to modulate one or more activities of an inorganic ion receptor and methods for treating diseases or disorders by modulating inorganic ion receptor activity. Preferably, the compound can mimic or block the effect of extracellular Ca.sub.2+ on a calcium receptor.

L5 ANSWER 19 OF 26 USPTAFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sub.2+ and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof,

targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

L5 ANSWER 20 OF 26 USPTAFULL on STN

AB The present invention features **calcilytic** compounds. "Calcilytic compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

L5 ANSWER 21 OF 26 USPTAFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

L5 ANSWER 22 OF 26 USPTAFULL on STN

AB The present invention features molecules which can modulate one or activities of an inorganic ion receptor. Preferably, the molecule can mimic or block the effect of extracellular Ca^{2+} on a calcium receptor. The preferred use of such molecules is to treat diseases or disorders by altering inorganic ion receptor activity, preferably calcium receptor activity.

L5 ANSWER 23 OF 26 USPTAFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

L5 ANSWER 24 OF 26 USPTAFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion

receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

L5 ANSWER 25 OF 26 USPATFULL on STN

AB The present invention features calcium receptor polypeptides and fragments thereof. Uses of a calcium receptor polypeptide include providing a polypeptide having the activity of a calcium receptor polypeptide. Calcium receptor polypeptide fragments can be used, for example, to generate antibodies to a calcium receptor polypeptide.

L5 ANSWER 26 OF 26 USPATFULL on STN

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

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IN Barmore Robert M; Callahan James F; Del Mar Eric G; Keenan Richard M;
Kotecha Nikesh R (GB); Lago Maria Amparo; Sheehan Derek; Southall Linda
Sue; Thompson Mervyn (GB); Van Wagenen Bradford C
PA NPS Pharmaceuticals Inc
Smithkline Beecham Corp

SmithKline Beecham PLC GB
(23499, 28684, 36782)

PI US 6022894 20000208 (CITED IN 002 LATER PATENTS)
AI US 1997-832984 19970404
RLI US 1996-629608 19960409 CONTINUATION-IN-PART ABANDONED
US 1996-32263 19961203 CONTINUATION-IN-PART
PRAI US 1996-32263P 19961203 (Provisional)
FI US 6022894 20000208
DT UTILITY; CERTIFICATE OF CORRECTION
CDAT 29 Jan 2002
FS CHEMICAL
GRANTED
OS CA 132:151556
MRN 008970 MFN: 0633
008970 0654
CLMN 30

L5 ANSWER 2 OF 26 USPATFULL on STN

AN 2003:300884 USPATFULL

TI **Calcilytic** compounds

IN Bhatnagar, Pradip K., King of Prussia, PA, UNITED STATES
Callahan, James F., Collegeville, PA, UNITED STATES
Lago, Amparo M., Collegeville, PA, UNITED STATES

PI US 2003212110 A1 20031113

AI US 2003-333096 A1 20030115 (10)
WO 2001-US22267 20010716

DT Utility

FS APPLICATION

LN.CNT 952

INCL INCLM: 514/336.000

INCLS: 514/345.000; 546/280.400; 546/300.000

NCL NCLM: 514/336.000

NCLS: 514/345.000; 546/280.400; 546/300.000

IC [7]

ICM: A61K031-4436

ICS: C07D049-02; C07D213-62; A61K031-44

L5 ANSWER 3 OF 26 USPATFULL on STN

AN 2003:251696 USPATFULL

TI Calcium receptor active compounds

IN Sakai, Teruyuki, Gunma, JAPAN
Takami, Atsuya, Gunma, JAPAN
Nagao, Rika, Gunma, JAPAN

PA NPS Pharmaceuticals, Inc. (non-U.S. corporation)

PI US 2003176485 A1 20030918

AI US 2002-243322 A1 20021121 (10)

RLI Continuation of Ser. No. US 2002-53133, filed on 17 Jan 2002, PENDING

DT Utility

FS APPLICATION

LN.CNT 10464

INCL INCLM: 514/416.000

INCLS: 514/617.000; 548/470.000; 564/164.000

NCL NCLM: 514/416.000

NCLS: 514/617.000; 548/470.000; 564/164.000

IC [7]

ICM: A61K031-4035

ICS: A61K031-165; C07D209-44

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 26 USPATFULL on STN

AN 2003:208165 USPATFULL

TI Calcium receptor-active compounds

IN Sakai, Teruyuki, Gunma, JAPAN
 Takami, Atsuya, Gunma, JAPAN
 Nagao, Rika, Gunma, JAPAN
 PA NPS Pharmaceuticals, Inc. (non-U.S. corporation)
 PI US 2003144526 A1 20030731
 AI US 2002-326713 A1 20021219 (10)
 RLI Division of Ser. No. US 2002-53133, filed on 17 Jan 2002, PENDING
 Continuation of Ser. No. US 1999-214552, filed on 6 Jan 1999, GRANTED,
 Pat. No. US 6362231 A 371 of International Ser. No. WO 1997-JP2358,
 filed on 8 Jul 1997, UNKNOWN
 PRAI JP 1997-107778 19970424
 JP 1996-350393 19961227
 JP 1996-178315 19960708
 DT Utility
 FS APPLICATION
 LN.CNT 10558
 INCL INCLM: 546/329.000
 INCLS: 548/503.000; 548/444.000; 549/460.000; 564/346.000
 NCL NCLM: 546/329.000
 NCLS: 548/503.000; 548/444.000; 549/460.000; 564/346.000
 IC [7]
 ICM: C07D213-26
 ICS: C07D277-62; C07D209-82; C07D209-14
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 26 USPATFULL on STN
 AN 2003:47795 USPATFULL
 TI **Calcilytic** compounds
 IN Del Mar, Eric G., Salt Lake City, UT, United States
 Barmore, Robert M., Salt Lake City, UT, United States
 Sheehan, Derek, Salt Lake City, UT, United States
 Van Wagenen, Bradford C., Salt Lake City, UT, United States
 Callahan, James F., Philadelphia, PA, United States
 Keenan, Richard M., Malvern, PA, United States
 Kotecha, Nikesh R., Thurmaston, UNITED KINGDOM
 Lago, Maria Amparo, Audobon, PA, United States
 Southall, Linda Sue, West Chester, PA, United States
 Thompson, Mervyn, Harlow Essex, UNITED KINGDOM
 PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
 corporation)
 SmithKline Beecham, PLC, Brentford, UNITED KINGDOM (non-U.S.
 corporation)
 SmithKline Beecham, Corp., Philadelphia, PA, United States (U.S.
 corporation)
 PI US 6521667 B1 20030218
 AI US 1998-132179 19980811 (9)
 RLI Division of Ser. No. US 1997-832984, filed on 4 Apr 1997, now patented,
 Pat. No. US 6022894 Continuation-in-part of Ser. No. US 1996-629608,
 filed on 9 Apr 1996, now abandoned
 PRAI US 1996-32263P 19961203 (60)
 DT Utility
 FS GRANTED
 LN.CNT 3269
 INCL INCLM: 514/653.000
 INCLS: 514/351.000; 514/357.000; 514/411.000; 514/432.000; 514/524.000;
 514/603.000; 514/649.000; 514/652.000; 546/300.000; 546/329.000;
 548/444.000; 549/023.000; 558/422.000; 564/085.000; 564/086.000;
 564/341.000; 564/349.000; 564/350.000; 564/351.000; 564/355.000;
 564/365.000; 564/367.000; 564/374.000; 564/378.000; 564/382.000
 NCL NCLM: 514/653.000
 NCLS: 514/351.000; 514/357.000; 514/411.000; 514/432.000; 514/524.000;
 514/603.000; 514/649.000; 514/652.000; 546/300.000; 546/329.000;

548/444.000; 549/023.000; 558/422.000; 564/085.000; 564/086.000;
564/341.000; 564/349.000; 564/350.000; 564/351.000; 564/355.000;
564/365.000; 564/367.000; 564/374.000; 564/378.000; 564/382.000

IC [7]

ICM: A01N033-02

EXF 564/341; 564/349; 564/350; 564/351; 564/85; 564/86; 564/367; 564/355;
564/363; 564/374; 564/378; 564/382; 558/422; 514/524; 514/603; 514/652;
514/653; 514/649; 514/654

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 26 USPATFULL on STN

AN 2003:24359 USPATFULL

TI **Calcilytic** compounds

IN Largo, Maria Amparo, Audubon, PA, UNITED STATES

Callahan, James Francis, Philadelphia, PA, UNITED STATES

Bhatnagar, Pradip Kumar, Exton, PA, UNITED STATES

Del Mar, Eric G., Salt Lake City, UT, UNITED STATES

Bryan, William M., Phoenixville, PA, UNITED STATES

Burgess, Joelle L., Trappe, PA, UNITED STATES

PI US 2003018203 A1 20030123

AI US 2002-181338 A1 20020717 (10)

WO 2001-US2402 20010124

DT Utility

FS APPLICATION

LN.CNT 1350

INCL INCLM: 548/561.000

INCLS: 558/418.000; 558/420.000; 560/037.000; 564/165.000; 564/348.000

NCL NCLM: 548/561.000

NCLS: 558/418.000; 558/420.000; 560/037.000; 564/165.000; 564/348.000

IC [7]

ICM: C07C255-56

ICS: C07C255-53; C07D207-30

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 26 USPATFULL on STN

AN 2002:201853 USPATFULL

TI **Calcilytic** compounds

IN Del Mar, Eric G., Salt Lake City, UT, United States

Barmore, Robert M., Salt Lake City, UT, United States

Sheehan, Derek, Salt Lake City, UT, United States

Van Wagenen, Bradford C., Salt Lake City, UT, United States

Callahan, James F., Philadelphia, PA, United States

Keenan, Richard M., Malvern, PA, United States

Kotecha, Nikesh R., Thurmaston, UNITED KINGDOM

Lago, Maria Amparo, Audobon, PA, United States

Southall, Linda Sue, West Chester, PA, United States

Thompson, Mervyn, The Pinnacles, UNITED KINGDOM

PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)

PI US 6432656 B1 20020813

AI US 1999-370097 19990806 (9)

RLI Division of Ser. No. US 1997-832984, filed on 4 Apr 1997, now patented,
Pat. No. US 6022894

PRAI US 1996-32263P 19961203 (60)

US 1997-42949P 19970407 (60)

DT Utility

FS GRANTED

LN.CNT 3139

INCL INCLM: 435/007.210

INCLS: 424/009.200; 424/009.600; 435/040.500; 435/960.000; 436/501.000;

436/519.000; 436/546.000; 436/811.000; 436/815.000

NCL NCLM: 435/007.210

NCLS: 424/009.200; 424/009.600; 435/040.500; 435/960.000; 436/501.000;
436/519.000; 436/546.000; 436/811.000; 436/815.000

IC

[7]

ICM: G01N033-554

ICS: A61K049-00

EXF 436/501; 436/811; 436/815; 436/546; 436/519; 435/7.21; 435/40.5;
435/960; 424/9.2; 424/9.6

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 26 USPATFULL on STN

AN 2002:199295 USPATFULL

TI Calcium receptor-active compounds

IN Sakai, Teruyuki, Gunma, JAPAN

Takami, Atsuya, Gunma, JAPAN

Nagao, Rika, Gunma, JAPAN

PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, UNITED STATES, 84108
(non-U.S. corporation)

PI US 2002107406 A1 20020808

AI US 2002-53133 A1 20020117 (10)

RLI Continuation of Ser. No. US 1999-214552, filed on 6 Jan 1999, PATENTED A
371 of International Ser. No. WO 1997-JP2358, filed on 8 Jul 1997,
UNKNOWN

PRAI JP 1996-178315 19960708

JP 1996-350393 19961227

JP 1997-10778 19970424

DT Utility

FS APPLICATION

LN.CNT 10642

INCL INCLM: 548/566.000

INCLS: 558/232.000; 558/390.000; 560/024.000; 560/038.000; 564/086.000;
564/164.000; 564/346.000

NCL NCLM: 548/566.000

NCLS: 558/232.000; 558/390.000; 560/024.000; 560/038.000; 564/086.000;
564/164.000; 564/346.000

IC

[7]

ICM: C07D027-335

ICS: C07C333-02; C07C311-30; C07C255-33; C07C237-30

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 26 USPATFULL on STN

AN 2002:186297 USPATFULL

TI Calcilytic compounds

IN Del Mar, Eric G., Salt Lake City, UT, UNITED STATES

Barmore, Robert M., Salt Lake City, UT, UNITED STATES

Sheehan, Derek, Salt Lake City, UT, UNITED STATES

Van Wagenen, Bradford C., Salt Lake City, UT, UNITED STATES

Callahan, James F., Philadelphia, PA, UNITED STATES

Keenan, Richard M., Malvern, PA, UNITED STATES

Kotecha, Nikesh R., Thurmaston, UNITED KINGDOM

Lago, Maria Amparo, Audobon, PA, UNITED STATES

Southall, Linda Sue, West Chester, PA, UNITED STATES

Thompson, Mervyn, The Pinnacles, UNITED KINGDOM

PA NPS Pharmaceuticals, Inc. (U.S. corporation)

PI US 2002099220 A1 20020725

AI US 2001-33001 A1 20011019 (10)

RLI Division of Ser. No. US 1998-132179, filed on 11 Aug 1998, PENDING
Continuation-in-part of Ser. No. US 1996-629608, filed on 9 Apr 1996,
ABANDONED

PRAI US 1996-32263P 19961203 (60)

DT Utility

FS APPLICATION

LN.CNT 3048

INCL INCLM: 546/329.000
INCLS: 560/038.000; 562/443.000; 564/164.000; 564/378.000
NCL NCLM: 546/329.000
NCLS: 560/038.000; 562/443.000; 564/164.000; 564/378.000
IC [7]
ICM: C07D213-26
ICS: C07C237-48

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 26 USPATFULL on STN
AN 2002:168247 USPATFULL
TI **Calcilytic** compounds
IN Lago, Amparo Maria, Audubon, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6417215 B1 20020709
WO 2000045816 20000810
AI US 2001-890310 20010726 (9)
WO 2000-US2676 20000202
20010706 PCT 371 date
PRAI US 1999-118240P 19990202 (60)
DT Utility
FS GRANTED
LN.CNT 1367
INCL INCLM: 514/381.000
INCLS: 514/652.000; 548/254.000; 558/422.000
NCL NCLM: 514/381.000
NCLS: 514/652.000; 548/254.000; 558/422.000
IC [7]
ICM: A61K031-135
ICS: A61K031-41
EXF 514/381; 514/652; 548/254; 558/422
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 11 OF 26 USPATFULL on STN
AN 2002:122786 USPATFULL
TI **Calcilytic** compounds
IN Bhatnagar, Pradip Kumar, Exton, PA, United States
Burgess, Joelle Lorraine, Phoenixville, PA, United States
Callahan, James Francis, Philadelphia, PA, United States
Calvo, Raul Rolando, Royersford, PA, United States
Del Mar, Eric G., Salt Lake City, UT, United States
Lago, Maria Amparo, Audubon, PA, United States
Nguyen, Thomas The, King of Prussia, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
NPS Pharmaceuticals, Salt Lake City, UT, United States (U.S. corporation)
PI US 6395919 B1 20020528
WO 9951569 19991014
AI US 2000-647793 20001005 (9)
WO 1999-US7722 19990408
20001005 PCT 371 date
PRAI US 1998-81093P 19980408 (60)
DT Utility
FS GRANTED
LN.CNT 2112
INCL INCLM: 558/414.000
INCLS: 560/036.000; 562/451.000
NCL NCLM: 558/414.000
NCLS: 560/036.000; 562/451.000
IC [7]

ICM: C07C255-03
ICS: C07C229-10
EXF 558/414; 548/473; 562/451; 560/36
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 12 OF 26 USPATFULL on STN
AN 2002:99608 USPATFULL
TI **Calcilytic** compounds and method of use
IN Bhatnagar, Pradip Kumar, Exton, PA, UNITED STATES
Callahan, James Francis, Philadelphia, PA, UNITED STATES
Del Mar, Eric G., Salt Lake City, UT, UNITED STATES
Lago, Maria Amparo, Audubon, PA, UNITED STATES
PA SmithKline Beecham Corporation (U.S. corporation)
PI US 2002052509 A1 20020502
AI US 2001-5490 A1 20011204 (10)
RLI Continuation of Ser. No. US 2000-647794, filed on 5 Oct 2000, PENDING A
371 of International Ser. No. WO 1999-US7760, filed on 8 Apr 1999,
UNKNOWN
PRAI US 1998-81087P 19980408 (60)
DT Utility
FS APPLICATION
LN.CNT 1533
INCL INCLM: 546/329.000
INCLS: 546/229.000; 548/566.000; 549/074.000; 549/492.000
NCL NCLM: 546/329.000
NCLS: 546/229.000; 548/566.000; 549/074.000; 549/492.000
IC [7]
ICM: C07D333-20
ICS: C07D037-34; C07D213-54; C07D211-82; C07D207-46
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 13 OF 26 USPATFULL on STN
AN 2002:63942 USPATFULL
TI Calcium receptor active compounds
IN Sakai, Teruyuki, Gunma, JAPAN
Takami, Atsuya, Gunma, JAPAN
Nagao, Rika, Gunma, JAPAN
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)
PI US 6362231 B1 20020326
WO 9801417 19980115
AI US 1999-214552 19990606 (9)
WO 1997-JP2358 19970708
19990617 PCT 371 date
PRAI JP 1996-178315 19960708
JP 1996-350393 19961227
JP 1997-107778 19970424
DT Utility
FS GRANTED
LN.CNT 10207
INCL INCLM: 514/654.000
INCLS: 514/655.000; 564/341.000
NCL NCLM: 514/654.000
NCLS: 514/655.000; 564/341.000
IC [7]
ICM: A61K031-145
ICS: A61P005-20; C07C321-28
EXF 564/341; 514/654; 514/655
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 14 OF 26 USPATFULL on STN
AN 2002:1232 USPATFULL

TI **Calcilytic** compounds
 IN Bhatnagar, Pradip, Exton, PA, United States
 Lago, Maria Amparo, Audubon, PA, United States
 PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S.
 corporation)
 PI US 6335338 B1 20020101
 WO 2000009491 20000224
 AI US 2001-762405 20010207 (9)
 WO 1999-US18377 19990812
 20010207 PCT 371 date
 PRAI US 1998-96336P 19980812 (60)
 DT Utility
 FS GRANTED
 LN.CNT 620
 INCL INCLM: 514/239.200
 INCLS: 544/163.000
 NCL NCLM: 514/239.200
 NCLS: 544/163.000
 IC [7]
 ICM: A61P019-10
 ICS: C07D265-30
 EXF 544/163; 514/239.2
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 15 OF 26 USPATEFULL on STN
 AN 2001:197043 USPATEFULL
 TI Calcium receptor-active molecules
 IN Van Wagenen, Bradford C., Salt Lake City, UT, United States
 Balandrin, Manuel F., Sandy, UT, United States
 DelMar, Eric G., Salt Lake City, UT, United States
 Nemeth, Edward F., Salt Lake City, UT, United States
 PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
 corporation)
 PI US 6313146 B1 20011106
 AI US 1995-484159 19950607 (8)
 RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
 Continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994
 Continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994,
 now abandoned Continuation-in-part of Ser. No. US 1993-141248, filed on
 22 Oct 1993, now abandoned Continuation-in-part of Ser. No. US
 1993-9384, filed on 23 Feb 1993, now abandoned Continuation-in-part of
 Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned
 Continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992
 Continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992,
 now abandoned Continuation-in-part of Ser. No. US 1991-749451, filed on
 23 Aug 1991, now abandoned
 DT Utility
 FS GRANTED
 LN.CNT 6744
 INCL INCLM: 514/337.000
 INCLS: 514/305.000; 514/336.000; 514/374.000; 514/384.000; 514/389.000;
 514/654.000
 NCL NCLM: 514/337.000
 NCLS: 514/305.000; 514/336.000; 514/374.000; 514/384.000; 514/389.000;
 514/654.000
 IC [7]
 ICM: A01N043-40
 ICS: A61K031-44
 EXF 564/337; 564/305; 564/336; 564/374; 564/384; 564/389; 514/654
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 16 OF 26 USPATEFULL on STN

AN 2001:163199 USPATFULL
 TI **Calcilytic** compounds
 IN Barmore, Robert M., Salt Lake City, UT, United States
 Bhatnagar, Pradip Kumar, Exton, PA, United States
 Bryan, William M., Phoenixville, PA, United States
 Burgess, Joelle Lorraine, Phoenixville, PA, United States
 Callahan, James Francis, Philadelphia, PA, United States
 Calvo, Raul Rolando, Royersford, PA, United States
 Del Mar, Eric G., Salt Lake City, UT, United States
 Lago, Maria Amparo, Audubon, PA, United States
 Nguyen, Thomas The, King of Prussia, PA, United States
 Sheehan, Derek, Salt Lake City, UT, United States
 Smith, Robert Lawrence, Lansdale, PA, United States
 Southall, Linda Sue, West Chester, PA, United States
 Van Wagenen, Bradford C., Salt Lake City, UT, United States
 PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
 PI US 6294531 B1 20010925
 WO 9845255 19981015
 AI US 1999-402310 19991001 (9)
 WO 1998-US6928 19980408
 19991001 PCT 371 date
 19991001 PCT 102(e) date
 PRAI US 1997-42724P 19970408 (60)
 US 1997-61327P 19971008 (60)
 US 1997-61329P 19971008 (60)
 US 1997-61330P 19971008 (60)
 US 1997-61333P 19971008 (60)
 US 1997-61331P 19971008 (60)
 DT Utility
 FS GRANTED
 LN.CNT 3114
 INCL INCLM: 514/227.500
 INCLS: 514/237.500; 514/239.500; 514/255.000; 514/330.000; 514/331.000;
 514/423.000; 514/424.000; 514/603.000; 514/619.000; 544/059.000;
 544/159.000; 544/162.000; 544/165.000; 544/383.000; 544/386.000;
 546/226.000; 546/232.000; 548/539.000; 548/542.000; 558/390.000;
 564/086.000
 NCL NCLM: 514/227.500
 NCLS: 514/237.500; 514/239.500; 514/255.010; 514/330.000; 514/331.000;
 514/423.000; 514/424.000; 514/603.000; 514/619.000; 544/059.000;
 544/159.000; 544/162.000; 544/165.000; 544/383.000; 544/386.000;
 546/226.000; 546/232.000; 548/539.000; 548/542.000; 558/390.000;
 564/086.000
 IC [7]
 ICM: C07C255-50
 ICS: C07C311-16; C07D295-26; C07D295-182
 EXF 564/220; 564/349; 564/86; 558/390; 544/59; 544/159; 544/162; 544/165;
 544/383; 544/386; 546/232; 546/226; 548/539; 548/542; 514/227.5;
 514/237.5; 514/239.5; 514/255; 514/330; 514/331; 514/423; 514/424;
 514/603; 514/619
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 L5 ANSWER 17 OF 26 USPATFULL on STN
 AN 2001:158282 USPATFULL
 TI **Calcilytic** compounds
 IN Bhatnagar, Pradip, Exton, PA, United States
 Lago, Maria Amparo, Audubon, PA, United States
 PA SmithKline Beecham Corporation, United States (U.S. corporation)
 PI US 6291459 B1 20010918
 WO 2000009132 20000224
 AI US 2001-762413 20010409 (9)

WO 1999-US18378 19990812
20010409 PCT 371 date
20010409 PCT 102(e) date

DT Utility
FS GRANTED
LN.CNT 679
INCL INCLM: 514/237.800
INCLS: 544/162.000
NCL NCLM: 514/237.800
NCLS: 544/162.000
IC [7]
ICM: A61K031-5375
ICS: C07D265-30
EXF 544/162; 514/237.8
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 18 OF 26 USPTFULL on STN
AN 2001:48117 USPATEFULL
TI Calcium receptor-active compounds
IN Van Wagenen, Bradford C., Salt Lake City, UT, United States
Moe, Scott T., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
DelMar, Eric G., Salt Lake City, UT, United States
Nemeth, Edward F., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)
PI US 6211244 B1 20010403
AI US 1995-546998 19951023 (8)
DT Utility
FS Granted
LN.CNT 3074
INCL INCLM: 514/649.000
INCLS: 564/182.000; 564/271.000; 564/374.000; 536/023.500
NCL NCLM: 514/649.000
NCLS: 536/023.500; 564/182.000; 564/271.000; 564/374.000
IC [7]
ICM: A61K031-135
ICS: A01N033-02; C07C209-48
EXF 564/374; 564/182; 564/271; 514/649; 536/23.5
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 19 OF 26 USPTFULL on STN
AN 2000:24677 USPATEFULL
TI Calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
DelMar, Eric G., Salt Lake City, UT, United States
Moe, Scott T., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)
The Brigham and Women's Hospital, Boston, MA, United States (U.S.
corporation)
PI US 6031003 20000229
AI US 1995-484719 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
which is a continuation-in-part of Ser. No. WO 1994-US12117, filed on 21
Oct 1994 Ser. No. Ser. No. US 1994-292827, filed on 19 Aug 1994, now
abandoned Ser. No. Ser. No. US 1993-141248, filed on 22 Oct 1993, now
abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned
which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12
Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US

1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility
FS Granted
LN.CNT 8955
INCL INCLM: 514/579.000
INCLS: 514/614.000; 514/607.000; 514/646.000; 514/649.000
NCL NCLM: 514/579.000
NCLS: 514/607.000; 514/614.000; 514/646.000; 514/649.000
IC [7]
ICM: A61K031-44
ICS: A61K031-135; A01N033-02; A01N037-18
EXF 514/2; 514/614; 514/579; 514/607; 514/646; 514/649
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 20 OF 26 USPATFULL on STN
AN 2000:15670 USPATFULL
TI Method of using **calcilytic** compounds
IN Del Mar, Eric G., Salt Lake City, UT, United States
Barmore, Robert M., Salt Lake City, UT, United States
Sheehan, Derek, Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Callahan, James F., Philadelphia, PA, United States
Keenan, Richard M., Malvern, PA, United States
Kotecha, Nikesh R., Thurmaston, United Kingdom
Lago, Maria Amparo, Audobon, PA, United States
Southall, Linda Sue, West Chester, PA, United States
Thompson, Mervyn, Harlow Essex, United Kingdom
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
SmithKline Beecham, Corp., Philadelphia, PA, United States (U.S. corporation)
SmithKline Beecham, PLC, Brentford, United Kingdom (non-U.S. corporation)
PI US 6022894 20000208
AI US 1997-832984 19970404 (8)
RLI Continuation-in-part of Ser. No. US 1996-629608, filed on 9 Apr 1996, now abandoned which is a continuation-in-part of Ser. No. US 1996-32263, filed on 3 Dec 1996
PRAI US 1996-32263P 19961203 (60)
DT Utility
FS Granted
LN.CNT 3170
INCL INCLM: 514/524.000
INCLS: 514/603.000; 514/651.000; 514/652.000; 514/654.000; 514/655.000; 564/349.000; 564/350.000; 564/351.000
NCL NCLM: 514/524.000
NCLS: 514/603.000; 514/651.000; 514/652.000; 514/654.000; 514/655.000; 564/349.000; 564/350.000; 564/351.000
IC [6]
ICM: A61K031-135
EXF 564/349; 564/350; 564/351; 514/652; 514/524; 514/603; 514/651; 514/654; 514/655
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 21 OF 26 USPATFULL on STN
AN 2000:1911 USPATFULL
TI Calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States

Balandrin, Manuel F., Sandy, UT, United States
 DelMar, Eric G., Salt Lake City, UT, United States
 Moe, Scott T., Salt Lake City, UT, United States
 PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
 corporation)
 The Brigham and Women's Hospital, Boston, MA, United States (U.S.
 corporation)
 PI US 6011068 20000104
 AI US 1994-353784 19941208 (8)
 RLI Continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994
 And a continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug
 1994, now abandoned And a continuation-in-part of Ser. No. US
 1993-141248, filed on 22 Oct 1993, now abandoned And a
 continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now
 abandoned which is a continuation-in-part of Ser. No. US 1993-17127,
 filed on 12 Feb 1993, now abandoned which is a continuation-in-part of
 Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a
 continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992,
 now abandoned which is a continuation-in-part of Ser. No. US
 1991-749451, filed on 23 Aug 1991, now abandoned
 DT Utility
 FS Granted
 LN.CNT 7466
 INCL INCLM: 514/654.000
 INCLS: 564/337.000; 564/366.000; 564/374.000; 564/384.000; 564/389.000
 NCL NCLM: 514/654.000
 NCLS: 564/337.000; 564/366.000; 564/374.000; 564/384.000; 564/389.000
 IC [6]
 ICM: A61K031-195
 ICS: C07C211-00; C07C213-00
 EXF 564/337; 564/366; 564/374; 564/384; 564/389; 514/654
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 22 OF 26 USPATFULL on STN
 AN 1999:163739 USPATFULL
 TI Calcium receptor-active molecules
 IN Nemeth, Edward F., Salt Lake City, UT, United States
 Van Wageningen, Bradford C., Salt Lake City, UT, United States
 Balandrin, Manuel F., Sandy, UT, United States
 Delmar, Eric G., Salt Lake City, UT, United States
 Moe, Scott T., Salt Lake City, UT, United States
 PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
 corporation)
 PI US 6001884 19991214
 AI US 1995-469204 19950606 (8)
 RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
 which is a continuation-in-part of Ser. No. WO 1994-US12177, filed on 21
 Oct 1994 And a continuation-in-part of Ser. No. US 1994-292827, filed on
 19 Aug 1994, now abandoned And a continuation-in-part of Ser. No. US
 1993-141248, filed on 22 Oct 1993, now abandoned And a
 continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now
 abandoned which is a continuation-in-part of Ser. No. US 1993-17127,
 filed on 12 Feb 1993, now abandoned which is a continuation-in-part of
 Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a
 continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992,
 now abandoned which is a continuation-in-part of Ser. No. US
 1991-749451, filed on 23 Aug 1991, now abandoned
 DT Utility
 FS Granted
 LN.CNT 1555
 INCL INCLM: 514/699.000
 INCLS: 564/387.000; 564/389.000; 564/390.000; 564/392.000; 564/655.000

NCL NCLM: 514/699.000
NCLS: 549/440.000; 564/387.000; 564/389.000; 564/390.000; 564/392.000
IC [6]
ICM: A01N035-00
EXF 564/387; 564/389; 564/390; 564/392; 564/164; 514/655; 514/319; 514/415;
514/418; 514/466; 514/524; 514/546; 514/620; 546/305; 546/306; 548/484;
548/491; 549/443; 558/422; 560/138
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 23 OF 26 USPATFULL on STN
AN 1999:121216 USPATFULL
TI Calcium receptor-active molecules
IN Brown, Edward M., Milton, MA, United States
Hebert, Steven C., Wellesley, MA, United States
Garrett, Jr., James E., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)
Brigham and Women's Hospital, Boston, MA, United States (U.S.
corporation)
PI US 5962314 19991005
AI US 1997-943986 19971003 (8)
RLI Continuation of Ser. No. US 1995-484565, filed on 7 Jun 1995, now
patented, Pat. No. US 5763569 which is a continuation-in-part of Ser.
No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part
of Ser. No. WO 1994-US12117, filed on 21 Oct 1994 Ser. No. Ser. No. US
1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. Ser. No. US
1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US
1993-9389, filed on 23 Feb 1993, now abandoned
DT Utility
FS Granted
LN.CNT 7882
INCL INCLM: 435/320.100
INCLS: 435/325.000; 435/243.000; 435/252.300; 536/023.100; 536/023.400;
536/023.500; 536/024.310; 530/300.000; 530/326.000; 530/350.000
NCL NCLM: 435/320.100
NCLS: 435/243.000; 435/252.300; 435/325.000; 530/300.000; 530/326.000;
530/350.000; 536/023.100; 536/023.400; 536/023.500; 536/024.310
IC [6]
ICM: C12N015-63
ICS: C12N015-11; C12N015-12; C07K007-00
EXF 435/69.1; 435/252.3; 435/320.1; 435/325; 435/243; 536/23.1; 536/23.4;
536/23.5; 536/24.31; 530/300; 530/326; 530/350
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 24 OF 26 USPATFULL on STN
AN 1999:4350 USPATFULL
TI Method of screening calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Brown, Edward M., Milton, MA, United States
Hebert, Steven C., Wellesley, MA, United States
Garrett, Jr., James E., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
Del Mar, Eric G., Salt Lake City, UT, United States
PA The Brigham and Women's Hospital, Inc., Boston, MA, United States (U.S.
corporation)
NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)
PI US 5858684 19990112
AI US 1995-480751 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
which is a continuation-in-part of Ser. No. US 1994-292827, filed on 19

Aug 1994, now abandoned And a continuation-in-part of Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

LN.CNT 7588

INCL INCLM: 435/007.200

INCLS: 435/065.100; 435/325.000; 435/252.300; 435/320.100; 435/007.100; 530/300.000; 530/324.000; 530/350.000; 536/023.100; 536/023.500

NCL NCLM: 435/007.200

NCLS: 435/007.100; 435/069.100; 435/252.300; 435/320.100; 435/325.000; 530/300.000; 530/324.000; 530/350.000; 536/023.100; 536/023.500

IC [6]

ICM: C12Q001-68

EXF 435/7.2; 435/65.1; 435/325; 435/252.3; 435/320.1; 530/300; 530/350; 530/324; 536/23.1; 536/23.5

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 25 OF 26 USPATFULL on STN

AN 1998:65348 USPATFULL

TI Calcium receptor-active molecules

IN Brown, Edward M., Milton, MA, United States

Hebert, Steven C., Wellesley, MA, United States

Garrett, Jr., James E., Salt Lake City, UT, United States

PA The Brigham and Women's Hospital, Inc, Boston, MA, United States (U.S. corporation)

NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)

PI US 5763569 19980609

AI US 1995-484565 19950607 (8)

RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned, said Ser. No. US -292827 which is a continuation-in-part of Ser. No. US -141248 which is a continuation-in-part of Ser. No. US -9389 And a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

LN.CNT 6942

INCL INCLM: 530/324.000

INCLS: 530/300.000; 530/376.000; 530/327.000; 530/329.000; 530/350.000; 536/023.100; 536/023.500; 435/007.100; 435/069.100; 435/252.300; 435/320.100

NCL NCLM: 530/324.000

NCLS: 435/007.100; 435/069.100; 435/252.300; 435/320.100; 530/300.000; 530/325.000; 530/326.000; 530/327.000; 530/350.000; 536/023.100; 536/023.500

IC [6]

ICM: C07K014-705

EXF 530/300; 530/350; 530/324; 530/326; 530/327; 530/329; 536/23.1;
536/23.5; 435/7.1; 435/69.1; 435/252.3; 435/240.1; 435/320.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 26 OF 26 USPATFULL on STN

AN 97:107219 USPATFULL

TI Calcium receptor-active molecules

IN Brown, Edward M., Milton, MA, United States

Fuller, Forrest H., Salt Lake City, UT, United States

Hebert, Steven C., Wellesley, MA, United States

Garrett, Jr., James E., Salt Lake City, UT, United States

PA The Brigham & Women's Hospital, Inc., Boston, MA, United States (U.S.
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NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.
corporation)

PI US 5688938 19971118

AI US 1995-485588 19950607 (8)

RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
which is a continuation-in-part of Ser. No. US 1993-9389, filed on 23
Feb 1993, now abandoned Ser. No. US 1993-141248, filed on 22
Oct 1993, now abandoned And Ser. No. US 1994-292827, filed on 19 Aug
1994, now abandoned which is a continuation-in-part of Ser. No. US
-141248 which is a continuation-in-part of Ser. No. US -9389 which is
a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993,
now abandoned which is a continuation-in-part of Ser. No. US
1992-934161, filed on 21 Aug 1992, now abandoned which is a
continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992,
now abandoned which is a continuation-in-part of Ser. No. US
1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

LN.CNT 6522

INCL INCLM: 536/023.500

INCLS: 435/069.100; 435/007.100; 435/290.100; 435/252.300; 435/320.100;
530/300.000; 530/350.000; 530/324.000; 530/326.000; 536/023.100;
536/024.310

NCL NCLM: 536/023.500

NCLS: 435/007.100; 435/069.100; 435/252.300; 435/320.100; 530/300.000;
530/324.000; 530/326.000; 530/350.000; 536/023.100; 536/024.310

IC [6]

ICM: C07K004-705

ICS: C12N015-12

EXF 435/7.1; 435/69.1; 435/240.1; 435/252.3; 435/320.1; 535/23.5; 535/23.1;
530/300; 530/350; 530/324; 530/326; 530/327; 530/329

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . Preferably, R.sub.3 and R.sub.4 are each independently a lower alkyl, more preferably, R.sub.3 and R.sub.4 are each independently methyl or **ethyl**;

DETD R.sub.5 is aryl. Preferably, R.sub.5 is either optionally substituted **naphthyl** or optionally substituted phenyl. More preferably, R.sub.5 is substituted phenyl having a substituent in the meta or para position and. . .

DETD . . . substituted. Preferably, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl.

DETD . . . an aryl, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, or optionally substituted tetrahydronaphthyl. Preferred, R.sub.1 substituents are each independently selected from the group consisting of: unsubstituted alkyl, unsubstituted alkenyl,. . .

DETD More preferred **calcilytic** compounds are Structure I derivatives where R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.6, Z, Y.sub.1 and Y.sub.2 are as described above for. . .

DETD R.sub.5 is either phenyl substituted with one to four independently selected substituents or an optionally substituted **naphthyl** having up to four independently selected substituents. R.sub.5 substituents are provided in Section II, supra., including preferred embodiments. More preferably. . . in a meta or para position, more preferably, the substituent present in a meta or para position is either methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy.

DETD The activity of different **calcilytic** compounds was measured using the Calcium Receptor Assay described below. Examples of compounds having an IC.sub.50.ltoreq.50 .mu.M include compounds 1,. . .

DETD R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or. . .

DETD R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or para position selected from the group consisting of: methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position;. . .

DETD The different **calcilytic** compounds described herein can have different stereochemistry around different groups. In an embodiment of the present invention the Structure I. . .

DETD The **calcilytic** compounds described herein can be formulated as a pharmaceutical composition to facilitate the administration of the compound to a patient. Preferred formulations contain a pharmaceutically acceptable carrier and a **calcilytic** compound as described in Section II, supra., including the different embodiments.

DETD . . . effects to patients suffering from a variety of diseases or disorders. Diseases or disorders which can be treated using a **calcilytic** compound are known in the art and can be identified using the present application as a guide. For example, diseases. . .

DETD Diseases and disorders which can be treated using the **calcilytic** compounds described herein include those due to different cellular defects related to calcium receptor activity in different cells, such

as. . .

DETD While **calcilytic** compounds of the present invention will typically be used to treat human patients, they may also be used to treat. . .

DETD Preferably, **calcilytic** compounds are used in the treatment of bone and mineral-related diseases or disorders. Bone and mineral-related diseases or disorders comprise. . . and mineral-related diseases or disorders include osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**. More preferably, **calcilytic** compounds are used to treat **osteoporosis**, a disease characterized by reduced bone density and an increased susceptibility to fractures. **Osteoporosis** is associated with aging, especially in women.

DETD One way of treating **osteoporosis** is by altering PTH secretion. PTH can have a catabolic or an anabolic effect on bone. Whether PTH causes a. . .

DETD As demonstrated by the Examples provided below, **calcilytic** compounds stimulate secretion of PTH. Such **calcilytic** compounds can be used to increase bone formation in a patient, for example, by intermittent dosing, thus achieving intermittent increases. . .

DETD The **calcilytic** compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical. . .

DETD The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

DETD The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .

DETD This example illustrates the use of the Calcium Receptor Inhibitor Assay. **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

DETD 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

DETD Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives include compounds which have both **calcilytic** activity and .beta.-adrenergic receptor activity. If desired, .beta.-adrenergic activity can be reduced using appropriate functional groups and structural modifications. Modifications. . .

DETD In one embodiment of the present invention the **calcilytic** compounds have an IC.sub.50.gtoreq.1.0 nM, at the .beta.-adrenergic receptor as measured using the ".beta.-Adrenergic Receptor Binding Assay" described below. In other embodiments, using the .beta.-Adrenergic Receptor Assay **calcilytic** compounds have an IC.sub.50.gtoreq.1.0 .mu.M, and IC.sub.50.gtoreq.10.0 .mu.M.

DETD This example illustrates the ability of different **calcilytic** compounds to exert a biological effect on PTH secretion. PTH secretion was determined using dissociated bovine parathyroid cells as described. . .

DETD General Procedures for the Preparation of **Calcilytic** Compounds

DETD The **calcilytic** compounds described by the present invention can be prepared using standard techniques. For example, an overall strategy for preparing preferred. . .

DETD . . . many of the compounds was carried out as follows: A solution of glycidyl ether (i.e., 1,2-epoxy-3-phenoxypropane, 1 mmol) and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, 1.5 mmol) in absolute ethanol (2 mL) is stirred overnight at 50-60.degree. C. The product is purified by. . .

DETD . . . washed with 10% aqueous NaHCO₃ (3.times.200 ml), dried over anhydrous sodium sulfate, filtered, and concentrated. Kugelrohr distillation (.about.100 microns) yielded 1-**naphthyl** glycidyl ether as a clear, colorless oil: GC/EI-MS, m/z (rel. int.) 200 (M.sup.+), 61), 184 (1), 169 (5), 157 (12),. . .

DETD A stirred solution of 1-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-fluorophenyl)ethylamine (334 mg, 2 mmol) in absolute ethanol (2 mL) was heated at. . .

DETD . . . mmol) were dissolved in 30 mL of water and enough acetone to maintain solubility at 0.degree. C. A solution of **ethyl** chloroformate (20.1 g, 185 mmol) in acetone (100 mL) was then added dropwise. An aqueous solution (95 mL) of sodium. . .

DETD Using the method of Example 5, supra, 1-**naphthyl** glycidyl ether (1.0 g, 5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.0 mg, 5.6 mmol) were used to prepare the free base of. . .

DETD Preparation of N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, Compound 28 ##STR19##

DETD Resolution of the Enantiomers (R) and (S)-N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 63 and 64 ##STR20##

DETD The enantiomers (R) and (S)-N-[2-hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine hydrochloride were prepared using the method of Example 7, supra. GC/EI-MS of each enantiomer gave m/z (rel. int.) 366 (M+1,. . . (21), 115 (11), 100 (4), 71 (21). The hydrochloride salt of each enantiomer was prepared by treatment of the free **amine** in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

DETD Using the method of Example 4, supra, 2-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (358 mg, 2 mmol) were used to prepare the free base of. . .

DETD Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 113 ##STR64##

DETD . . . washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by preparative TLC using **ethyl** acetate/hexane as the elutant. The yield of 1-**ethyl**-1-methyl-2-(4-hydroxyphenyl)nitroethane was 0.21 grams.

DETD . . . a suspension of 40% (wt/wt) potassium fluoride on alumina (0.73 g, 5 mmol) in 3 mL of acetonitrile were added 1-**ethyl**-1-methyl-2-(4-hydroxyphenyl)nitroethane (0.21 g, 1.0 mmol) and iodomethane (0.21 g, 1.5 mmol). The reaction was stirred at room temperature for 4 days. . . washed with sodium bisulfite, sodium carbonate, and saturated brine, then dried over anhydrous sodium sulfate and concentrated. The yield of 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)nitroethane was 0.183 g.

DETD . . . 5 mL of methanol, followed by the addition of sodium borohydride (0.05 g, 1.2 mmol). After stirring for 5 minutes, 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)nitroethane (0.18 g, 0.807 mmol) in 3 mL of methanol was added, and stirred for 5 minutes. Sodium borohydride (0.11 g,. . . hydroxide. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine was 0.127 grams.

DETD Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.086 g, 0.57 mmol) and 1-**ethyl**-1-methyl-2-(4-

methoxyphenyl)ethylamine (0.11 g, 0.57 mmol) were used to prepare 90 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-naphthyl)ethylamine Hydrochloride, Compound 120 ##STR71##

DETD Using the method of Example 52, supra, 2-aminomethylnaphthalene (2.51 g, 16 mmol) was used to prepare 1.9 g of 1,1-dimethyl-2-(2-naphthyl)ethylamine.

DETD Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.163 g, 1.1 mmol) and 1,1-dimethyl-2-(2-naphthyl)ethylamine (0.26 g, 1.3 mmol) were used to prepare 243 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (230 mg, 1.5 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 130 mg of the title. . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 88 mg of a white. . .

DETD Synthesis of (R/S)-1-[[2,2-dimethyl(4'methoxy)phenethyl]]amino-2-hydroxy-4(1'-naphthyl)-butane, Compound 162 ##STR83##

DETD . . . with CH₂Cl₂ and was extracted with sodium sulfite (aqueous) and NaHCO₃ (aqueous), dried over MgSO₄, filtered and evaporated to give 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) that was carried without further purification.

DETD A solution of 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) and 1,1-dimethyl-2(4-methoxyphenyl) ethylamine (985 mg, 5.5 mmol) in ethanol (25 mL) was heated at reflux for 12 hours.. . . addition of ether, crystals formed and were subsequently collected and dried in a vacuum oven to give 1.4 g of (R/S)-1-[[2,2-dimethyl-(4'methoxy)phenethyl]]amino-2-hydroxy-4(1'-naphthyl)-butane. ESMS [(M+H)⁺=378, .sup.1H NMR (CDCl₃, 360 MHz) @300.degree. K .delta.8.06 (1H, d of d), 7.83 (1H, d of d), 7.78-7.61. . .

DETD N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)ethyl]amine Hydrochloride Salt Compound 165 ##STR86##

DETD e) N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)ethyl]amine hydrochloride salt.

DETD Compound 92: N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(1-naphthyl)ethylamine.

CLM What is claimed is:

1. A method for identifying a calcilytic compound that optimally inhibits one or more calcium receptor activities in a particular cell type, the method comprising: contacting a particular type of calcium receptor-bearing cell with a calcilytic compound having the formula: ##STR87## wherein R.sub.1 is selected from the group consisting of: aryl, longer-length alk, and cyclo-alk; R.sub.2. . . the effect of said compound on a calcium receptor activity of said particular type of calcium receptor-bearing cell, wherein said calcilytic compound is identified by the inhibition of said calcium receptor activity.

L2 ANSWER 8 OF 26 USPTATFULL on STN

AN 2002:199295 USPTATFULL

TI Calcium receptor-active compounds

IN Sakai, Teruyuki, Gunma, JAPAN
Takami, Atsuya, Gunma, JAPAN
Nagao, Rika, Gunma, JAPAN

PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, UNITED STATES, 84108
(non-U.S. corporation)
PI US 2002107406 A1 20020808
AI US 2002-53133 A1 20020117 (10)
RLI Continuation of Ser. No. US 1999-214552, filed on 6 Jan 1999, PATENTED A
371 of International Ser. No. WO 1997-JP2358, filed on 8 Jul 1997,
UNKNOWN
PRAI JP 1996-178315 19960708
JP 1996-350393 19961227
JP 1997-10778 19970424
DT Utility
FS APPLICATION
LREP Michael A. Whittaker, FOLEY & LARDNER, P.O. Box 80278, San Diego, CA,
92138-0278
CLMN Number of Claims: 56
ECL Exemplary Claim: 1
DRWN 94 Drawing Page(s)
LN.CNT 10642

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl,
bis(arylmethyl)amino, bis(heteroarylmethyl)amino and
arylmethyl(heteroarylmethyl) amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl,
sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8
and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

SUMM . . . one or more of the rings has a completely conjugated pielectron
system. Examples, without limitation, of aryl groups, are phenyl,
naphthyl, anthracenyl, phenanthrenyl, fluorenyl, and indanyl.
The aryl group may be substituted or unsubstituted. When substituted,
the substituted group(s) is preferably. . .

SUMM . . . or more halogens and, combined, unsubstituted cycloalkyl and
cycloalkenyl. Also preferably, Ar.sub.1 is selected from the group
consisting of phenyl, **naphthyl**, indolyl, fluorenyl,
dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl,
pyridin-4-yl, quinolin-2-yl and dibenzylamino and Ar.sub.2 is selected
from the group consisting of phenyl, **naphthyl**, quinolin-4-yl,
pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl,
furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl.
More preferably, Ar.sub.1 is phenyl substituted with one. . . alkoxy,
trihalomethoxy, trihaloacetyl and nitro, and Ar.sub.2 is selected from
the group consisting of optionally substituted phenyl and optionally
substituted **naphthyl**. Even more preferably, Ar.sub.2 is
3-methoxyphenyl or unsubstituted **naphthyl**. Preferably, R.sup.8
is hydrogen, R.sup.9 is methyl and X is oxygen or sulfur.

SUMM . . . halogen, unsubstituted lower alkoxy, lower alkoxy substituted
with one or more halogens, nitro, dimethylamino and unsubstituted

phenyl, and optionally substituted **naphthyl**; and Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from. . . one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted **naphthyl**.

SUMM . . . substituted with one or more halogens and lower alkoxy substituted with one or more halogens; and Ar.sub.6 is 3-methoxyphenyl or .alpha.-**naphthyl**, more preferably, a-**naphthyl**. Also preferably, Ar.sub.5 is dibenzylamino, benzyl(naphthylmethyl) amino or benzyl (pyridylmethyl)amino optionally substituted with one or more groups independently selected from. . . lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens, and Ar.sub.6 is **naphthyl** or methoxyphenyl. More preferably, Ar.sub.5 is dibenzylamino optionally substituted with unsubstituted alkyl, and Ar.sub.6 is a-**naphthyl**.

SUMM . . . the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (calcimimetic modulation) or blocking the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (**calcilytic** modulation); preferably calcimimetic modulation.

SUMM . . . aspect, the present invention provides a method for the treatment or prevention of primary and secondary hyperparathyroidism, renalosteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering a therapeutically effective amount of a compound of this invention to a patient.

SUMM . . . affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, **osteoporosis** is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic. . . levels (e.g., a parathyroid cell ionmimetic) can retard bone loss and, thus, result in beneficial effects to patients suffering from **osteoporosis**.

SUMM . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from **osteoporosis**.

SUMM . . . modulates one or more effects of an inorganic ion receptor. Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and **calcilytics**.

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. **Calcilytics** are ionlytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium. . .

SUMM . . . preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis**, renalosteodystrophy and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as.

SUMM . . . Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism, renalosteodystrophy and **osteoporosis**.

DETD . . . mimic or block an effect of extracellular Ca.sup.2+ on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and **calcilytics**.

DETD [0233] Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 mM, and even more. . .

DETD [0235] In another preferred embodiment the calcium receptor modulating agent is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . .

DETD . . . need not possess all the biological activities of extracellular Ca.sup.2+, but, rather, at least one such activity is mimicked. Similarly, **calcilytics** need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular Ca.sup.2+ to exert their. . .

DETD [0255] B. **Calcilytics**

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium sulfate. . .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was added to the reaction mixture. Then the mixture was stirred at room temperature, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 17.31 g (87.8%) of colorless prism crystals 48.

DETD . . . 6 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 36.8 g (82.8%) of colorless prism crystals 49.

DETD . . . C. for 2.5 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 52.

DETD . . . (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 162.7 mg (0.95 mmol, 2.0 moleq.) of (R)-1-(1-naphthyl)ethylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an. . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 53.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 723.4 mg (87.0%) of a colorless oil 55.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium

sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 56.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 202.4 mg (73.3%) of a colorless prism crystals 58.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 59.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 824.0 mg (84.9%) of a colorless oil 61.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 222.6 mg (87.1%) of a colorless oil 62.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 884.2 mg (91.1%) of a colorless oil 64.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 229.3 mg (89.7%) of a colorless oil 65.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 876.5 mg (90.3%) of a colorless oil 67.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl

acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 293.1 mg (87.2%) of a colorless oil 68.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 804.3 mg (77.0%) of colorless prism crystals 70.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 880.8 mg (89.5%) of a colorless oil 71.

DETD . . . temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 551.8 mg (100%) of a colorless oil 73.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 230.8 mg (91.3%) of a colorless oil 74.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 241.3 mg (45.9%) of a colorless oil 76.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 209.8 mg (69.7%) of a colorless oil 77.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 586 mg (61.4%) of a colorless oil 79.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 265.1 mg (82.8%) of a colorless oil 80.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 564.9 mg (82.5%) of colorless prism crystals 82.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 311.9 mg (83.8%) of colorless prism crystals 83.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 85.

DETD . . . acidified with a 5% aqueous solution of hydrochloric acid. Then the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 86.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 615.4 mg (98.5%) of colorless prism crystals 87.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with **ethyl** acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 76.3 mg (82.6%) of a colorless oil 88.

DETD [0390] To a solution of 600 mg (3.5 mmol) of (R)-1-(1-naphthyl)ethylamine 89 in 5 ml of methylene chloride were added 580.3 mg (d=1.176, 3.85 mmol, 1.1 moleq.) of ethylmalonyl chloride and . . . and dried over sodium sulfate. After distilling off the solvent, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 662.9 mg (66.5%) of colorless prism crystals 90.

DETD . . . concentrated, acidified with a 5% aqueous solution of

hydrochloric acid. The reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 596.0 mg (99.8%) of colorless prism crystals 91.

DETD . . . (1.56 mmol) of the compound 91 in 5 ml of dimethylformamide were added 293.2 mg (1.71 mmol, 1.1 moleq.) of (R)-1-(1-**naphthyl**)ethylamine and 359.2 mg (1.87 mmol, 1.2 moleq.) of WSC.times.HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 615.1 mg (96.4%) of colorless prism crystals 92.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with **ethyl** acetate. The hydrochloric acid layer was made alkaline by adding a 5%-aqueous solution of sodium hydroxide and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 82.0 mg (88.0%) of a colorless oil 93.

DETD [0399] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 361.8 mg (80.0%) of the compound 102 as colorless prisms.

DETD . . . a solution of the above compound 102 (125.8 mg, 0.38 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0403] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.1 mg (89.5%) of the compound 103 as a colorless oil.

DETD [0407] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, n-hexane/**ethyl** acetate] to thereby give the compound 105 (723.4 mg, 87.0%) as a colorless oil. Compound 106:

DETD . . . a solution of the above compound 105 (106.2 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (48.4 mg, 0.35 mmol, 1.2 mol eq.) and the resulting mixture was stirred. . .

DETD [0409] After the completion of the reaction, the reaction mixture was

poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 33.7 mg (76.1%) of the compound 106 as a colorless oil.

DETD [0413] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 804.3 mg (77.0%) of the compound 108 as colorless prisms.

DETD . . . a solution of the above compound 108 (106.9 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0416] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.2 mg (58.3%) of the compound 109 as a colorless oil.

DETD [0420] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 586 mg (61.4%) of the compound 111 as a colorless oil.

DETD . . . a solution of the above compound 111 (65.3 mg, 0.26 mmol, 1.5 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (29.3 mg, 0.17 mmol) and potassium carbonate (35.5 mg, 0.26 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0424] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 36.5 mg (62.0%) of the compound 112 as a colorless oil.

DETD [0427] To a solution of (R)-(+)-1-(1-**naphthyl**)ethylamine (600 mg, 3.5 mmol) in dichloromethane (5 ml) were added ethylmalonyl chloride 113 (580.3 mg, 3.85 mmol, 1.1 mol eq.). . .

DETD . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 662.9 mg (66.5%) of the compound 114 as colorless prisms.

DETD . . . the reaction mixture was concentrated, acidified with a 5% aqueous solution of hydrochloric acid, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed successively with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 659.5 mg of the compound 115 as

colorless prisms.

DETD [0435] To a solution of the above compound 115 (50 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (45.0 mg, 0.21 mmol, 1.1 mol eq.) and WSC.multidot.HCl (44.9 mg, 0.23 mmol, 1.2 mol eq.) and the resulting mixture. . .

DETD [0436] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 61.6 mg (70.5%) of the compound 116 as colorless prisms.

DETD . . . into the reaction mixture. Then the mixture was acidified with a 5% aqueous solution of hydrochloric acid and extracted with **ethyl** acetate. The layer of the 5% aqueous solution of hydrochloric acid was made alkaline by adding a 5% aqueous solution of sodium hydroxide and then extracted with **ethyl** acetate. After washing with water and a saturated aqueous solution of sodium chloride and drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 18.0 mg (88.0%) of the compound 117 as a colorless oil.

DETD . . . After the completion of the reaction, ammonium chloride was added thereto in excess and the reaction mixture was extracted with **ethyl** acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 16.0 g of the compound 119.

DETD [0447] After cooling by allowing to stand, it was purified by column chromatography and eluted with **ethyl** acetate/n-hexane to thereby give 700 mg of the compound 120.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 1.5 g of the compound 122.

DETD [0454] The above compound 122 (150 mg, 0.51 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (104.5 mg, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (3 ml) and then allowed to stand at room. . .

DETD Synthesis of K-2027 (N-{5-[(4-chlorophenyl)thio]pentyl}N-[(1R)-1-(1-**naphthyl**)**ethyl**amine])

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (241 mg, 1.74 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.31 ml, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . C. for 24 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.70 g, 12.3 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.45 ml, 2.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2052 (N-{5-[(4-fluorophenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)**ethyl**amine])

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (300 mg, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . temperature for 1 hour. After confirming the completion of the

reaction by TLC, potassium carbonate (247 mg, 1.79 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2076 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(5-[[4-(trifluoromethyl)phenyl]thio]pentyl)amine)
 DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (200 mg, 1.45 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.28 ml, 1.73 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2087 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[[3-(trifluoromethyl)phenyl]thio]butyl)amine)
 DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2117 ((R)-N-[1-(1'-**naphthyl**)ethyl]-2-(2',5'-dichlorophenylthio)ethylamine)
 DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (4.0 g, 28.9 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (3.70 ml, 22.9 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD [0549] The compound thus obtained (50 mg, 0.20 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (41.0 mg, 0.24 mmol, 1.2 mol eq.) were dissolved in chloroform-methanol (2 ml) and allowed to stand at room temperature. . .

DETD Synthesis of K-2246 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[[4-(trifluoromethyl)phenyl]thio]butyl)amine)
 DETD . . . reaction by TLC, 5 ml of acetonitrile, 693 mg (5.01 mmol) of potassium carbonate and 0.49 ml (2.96 mmol) of (R)-(+)-1-(1-**naphthyl**)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD . . . reaction by TLC, 8 ml of acetonitrile, 853 mg (6.17 mmol) of potassium carbonate and 0.60 ml (3.63 mmol) of (R)-(+)-1-(1-**naphthyl**)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD Synthesis of K-2243 (N1,N1-di(4-chlorobenzyl)-3-[(1R)-1-(1-**naphthyl**)ethyl]amino)propanamide)
 DETD [0561] After the completion of the reaction, the solvent was distilled off under reduced pressure. **Ethyl** acetate and water were poured into the residue, and filtered through celite. The residue was washed with **ethyl** acetate and then the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . Hz, Ar--H). 100 mg (0.31 mmol) of the above-mentioned compound 125 and 64.2 mg (0.38 mmol, 1.2 mol eq.) of (R)-(+)-(1-**naphthyl**)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2257 (N1,N1-di[4-(trifluoromethoxy)benzyl]-3-[(1R)-1-(1-**naphthyl**)ethyl]amino)propanamide)
 DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. **Ethyl** acetate and water were poured into the residue and filtered through celite. The residue was washed with **ethyl** acetate and then the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium

chloride and dried over sodium sulfate. After. . .

DETD [0569] 450 mg (1.07 mmol) of the above-mentioned compound 127 and 220.7 mg (1.29 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2259 (N1,N1-di[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . m, Ar--H). 800 mg (2.06 mmol) of the above-mentioned compound 129 and 424.0 mg (2.48 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2247 (N1-benzyl-N1-(4-chlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0577] The conjugated ketone compound 202 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0581] The conjugated ketone compound 204 (105.8 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0585] The conjugated ketone compound 206 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD Synthesis of K-2250 (N1-benzyl-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through

celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0589] The conjugated ketone compound 208 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0593] The conjugated ketone compound 210 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0597] The conjugated ketone compound 212 (100 mg, 0.35 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (71.8 mg, 0.42 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0601] The conjugated ketone compound 214 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0605] The conjugated ketone compound 216 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with

ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0609] The conjugated ketone compound 218 (800 mg, 1.63 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (33.7 mg, 1.95 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0613] The conjugated ketone compound 220 (1 g, 3.13 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (642.2 mg, 3.75 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2262 (N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0617] The conjugated ketone compound 222 (500 mg, 1.56 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (321.1 mg, 1.88 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2264 (N1-(3,4-dichlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0623] The conjugated ketone compound 224 (800 mg, 2.06 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (387.7 mg, 2.26 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2265 (N1,N1-di(3,4-dichlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 225 (712.2 mg, 74.3%).

DETD [0629] The conjugated ketone compound 226 (280 mg, 0.72 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (148 mg, 0.864 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2266 (N1-(4-chlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled

off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0635] The conjugated ketone compound 228 (800 mg, 2.26 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (425.4 mg, 2.48 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2267 (N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0641] The conjugated ketone compound 230 (600 mg, 1.69 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (347.2 mg, 2.03 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2270 (N1,N1-di(4-methoxybenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0647] The conjugated ketone compound 232 (450 mg, 1.45 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (297 mg, 1.74 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2272 (N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]-amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 233 (777.3 mg, 78.2%). MS m/z: 350, .sup.1H-NMR d: 3.76 (2H, s, . . .

DETD [0652] The conjugated ketone compound 234 (350 mg, 0.87 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (178 mg, 1.04 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2283 (N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]-amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane **ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 235 (1.092 g, 98.1%).

DETD [0658] The conjugated ketone compound 236 (400 mg, 1.08 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (222 mg, 1.30 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2289 (N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-([(1R)-1-(1-**naphthyl**) **ethyl**] amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel,

hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 237 (711.8 mg, 74.8%).

- DETD [0664] The conjugated ketone compound 238 (414 mg, 1.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (270 mg, 1.57 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .
- DETD Synthesis of K-2290 (N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
- DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .
- DETD [0670] The conjugated ketone compound 240 (874.7 mg, 2.50 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (513.9 mg, 3.00 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .
- DETD Synthesis of K-2291 (N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
- DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .
- DETD [0676] The conjugated ketone compound 242 (500 mg, 1.49 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (307 mg, 1.79 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .
- DETD Synthesis of K-2294 (N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
- DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .
- DETD [0682] The conjugated ketone compound 244 (1.5587 g, 4.67 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (959.6 mg, 5.60 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .
- DETD Synthesis of K-2299 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
- DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .
- DETD [0688] The conjugated ketone compound 246 (1.4568 g, 4.36 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (896.8 mg, 5.24 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .
- DETD Synthesis of K-2300 (N1,N1-di(4-methylbenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
- DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 247 (819.4 mg, 88.2%).
- DETD [0694] The conjugated ketone compound 248 (400 mg, 1.43 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (295 mg, 1.72 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at

room temperature for. . .

DETD Synthesis of K-2309 (N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-
 ([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The
 oil thus obtained was purified by column chromatography [silica gel,
 hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless
 oil 249 (827.0 mg, 76.8%).

DETD [0700] The conjugated ketone compound 250 (692.4 mg, 1.98 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (407 mg, 2.37 mmol, 1.2 mol
 eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at
 room temperature for. . .

DETD Synthesis of K-2310 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)
 benzyl]-3-([(1R)-1-(1-naphthyl)ethyl
]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The
 oil thus obtained was purified by column chromatography [silica gel,
 hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless
 oil 251 (979.1 mg, 80.4%).

DETD [0706] The conjugated ketone compound 252 (685.1 mg, 1.96 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (403 mg, 2.36 mmol, 1.2 mol
 eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at
 room temperature for. . .

DETD . . . and the solvent was distilled off under reduced pressure. The
 oil thus obtained was purified by column chromatography [silica gel,
 hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless
 oil 253 (944.0 mg, 83.4%).

DETD [0712] The conjugated ketone compound 254 (612.8 mg, 1.68 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (345 mg, 2.01 mmol, 1.2 mol
 eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at
 room temperature for. . .

DETD [0718] The conjugated ketone compound 256 (260.2 mg, 0.88 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (180 mg, 1.05 mmol, 1.2 mol
 eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at
 room temperature for. . .

DETD Synthesis of K-2280 (N-{5-[(4-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-
 naphthyl)ethyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the
 reaction by TLC, potassium carbonate (931 mg, 6.75 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (0.52 ml, 3.22 mmol) were
 added at the same temperature to the reaction system. Further, the
 reaction mixture was stirred. . .

DETD Synthesis of K-2281 (N-[(1R)-1-(1-naphthyl)ethyl
]-N-{4-[(2,4,5-trichlorophenyl)thio]butyl}amine)

DETD . . . temperature for 3 hours. After confirming the completion of the
 reaction by TLC, potassium carbonate (545 mg, 3.94 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (0.41 ml, 3.94 mmol) were
 added at the same temperature to the reaction system. Further, the
 reaction mixture was stirred. . .

DETD Synthesis of K-2282 (N-[(1R)-1-(1-naphthyl)ethyl
]-N-{5-[(2,4,5-trichlorophenyl)thio]pentyl}amine)

DETD . . . temperature for 2.5 hours. After confirming the completion of
 the reaction by TLC, potassium carbonate (1.00 g, 7.25 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (0.69 ml, 4.27 mmol) were
 added at the same temperature to the reaction system. Further, the
 reaction mixture was stirred. . .

DETD Synthesis of K-2287 (N-[(1R)-1-(1-naphthyl)ethyl
]-N-{4-[(4-(trifluoromethoxy)phenyl)thio]butyl}amine)

DETD . . . temperature for 5 hours. After confirming the completion of the
 reaction by TLC, potassium carbonate (710 mg, 5.14 mmol) and
 (R)-(+)-1-(1-naphthyl)ethylamine (0.53 ml, 3.28 mmol) were
 added at the same temperature to the reaction system. Further, the
 reaction mixture was stirred. . .

DETD Synthesis of K-2288 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[4-(trifluoromethoxy)phenyl]thio)pentyl)amine)

DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (770 mg, 5.57 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.58 ml, 3.59 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2293 (N-[4-[(4-chlorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (775 mg, 5.61 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.62 ml, 3.84 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2240 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(3-[4-(trifluoromethyl)phenyl]thio)propyl)amine)

DETD Synthesis of K-2263 (N-[4-[(4-fluorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2269 (N-[4-[(3-methoxyphenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2271 (N-[[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2279 (N-[[5-(3-methoxyphenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2284 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)pentyl)amine)

DETD Synthesis of K-2286 (N-[6-[(4-chlorophenyl)thio]hexyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2292 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(7-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)heptyl)amine)

DETD Synthesis of K-2296 (N-[[5-(2,5-dichlorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2297 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)butyl)amine)

DETD Synthesis of K-2298 (N-[4-[(2,5-dichlorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2301 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(6-([4-(trifluoromethoxy)phenyl]thio)hexyl)amine)

DETD Synthesis of K-2302 (N-[4-[(2,4-dimethylphenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2303 (N-[5-[(2,4-dimethylphenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2304 (N-[4-[(4-methylphenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2305 (N-[5-[(4-methylphenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine respectively by 3-trifluoromethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-methylbenzylamine. m/z=355.

DETD . . . synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the (R)-(+)-3-methoxy-.alpha.-benzylmethylamine by (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but

replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=419.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=349.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,4-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 2,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-a-benzylmethylanine respectively by 2,6-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,6-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylanine respectively by 2,6-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-

.alpha.-benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl) ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-*a*-benzylmethylamine respectively by 3,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-*a*-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DET . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.
m/z=391.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,5-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-2.alpha.-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl) ethylamine.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-*a*-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DET D . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,5-dimethylthiophenol,

[illegible]

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=398.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=444, 446.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=447.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=408.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=422.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-

naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=375.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-trifluoromethoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=391.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2-chlorobenzylmercaptan and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 2-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-chlorobenzylmercaptan and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=355.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-quinolinethiol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine. 400MHZ-^{sup}1H-NMR 8.18 (1H, d, J=8.0 Hz), 7.83-7.87 (3H, m), 7.73 (1H, d, J=8.0 Hz), 7.65-7.70 (2H, m), 7.56-7.60 (1H, m), . . .

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-quinolinethiol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-quinolinethiol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-methylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-methylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=424.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=438.

DETD . . . potassium carbonate (4.04 g) was added thereto. After 1 hour, water was added and the resulting mixture was extracted with **ethyl** acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crystals thus obtained were washed with chloroform to thereby give N-(2-(2',5'-dichlorophenylthio)**ethyl**phthalimide (F-8) (8.28 g). MS m/z: 351 (M.^{sup}+).

DETD [1274] N-(2-(2',5'-Dichlorophenylthio)**ethyl**phthalimide (F-8) (7.06 g) was added to ethanol (120 ml). After further adding hydrazine monohydrate (6.9 ml), the obtained mixture was. . .

DETD . . . ice-cooling. Then the mixture was brought to room temperature and stirred for 15 hours. The reaction mixture was concentrated and **ethyl** acetate and water were added thereto. The insoluble matters were filtered off and the organic layer was washed with a. . . sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol=50:1) to thereby give (.-)-N-(1-(3-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-12) (146 mg).

DETD [1277] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethoxyacetophenone to thereby give (.-)-N-(1-(3,4-dimethoxyphenyl)**ethyl**

)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 385 (M.sup.+).

DETD [1278] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-methylacetophenone to thereby give (.-.-)-N-(1-(3-methylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-14). MS m/z: 339 (M.sup.+).

DETD [1279] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-methylacetophenone to thereby give (.-.-)-N-(1-(4-methylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 339 (M.sup.+).

DETD [1280] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4',5'-trimethoxyacetophenone to thereby give (.-.-)-N-(1-(3,4,5-trimethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-16). MS m/z: 415 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxyacetophenone to thereby give (.-.-)-N-(1-(4-hydroxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-17). MS m/z: 341 (M.sup.+).

DETD [1282] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethyl)acetophenone to thereby give (.-.-)-N-(1-(3-trifluoromethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-18). MS m/z: 393 (M.sup.+).

DETD [1283] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxy-3'-methoxyacetophenone to thereby give (.-.-)-N-(1-(4-hydroxy-3'-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-21). MS m/z: 371 (M.sup.+).

DETD [1284] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-bromoacetophenone to thereby give (.-.-)-N-(1-(4-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-22). MS m/z: 405 (M.sup.+).

DETD [1285] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-bromoacetophenone to thereby give (+)-N-(1-(3-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-23). MS m/z: 405 (M.sup.+).

DETD [1286] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-bromoacetophenone to thereby give (+)-N-(1-(2-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-24). MS m/z: 405 (M.sup.+).

DETD [1287] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dihydroxyacetophenone to thereby give (.-.-)-N-(1-(3,4-dihydroxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-29). MS m/z: 357 (M.sup.+).

DETD . . . procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dichloroacetophenone to thereby give (.-.-)-N-(1-(2,5-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-30). MS m/z: 353 (M.sup.+).

DETD [1289] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoro-4'-methoxyacetophenone to thereby give (.-.-)-N-(1-(3-fluoro-4-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-31). MS m/z: 373 (M.sup.+).

DETD [1290] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethoxy)acetophenone to thereby give (.-.-)-N-(1-(3-trifluoromethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 409 (M.sup.+).

DETD [1291] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethylacetophenone to thereby give (.-.-)-N-(1-(3,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-48). MS m/z: 353 (M.sup.+).

DETD [1292] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-chloroacetophenone to thereby give (.-.-)-N-(1-(2-chlorophenyl)**ethyl**)-2-(2',5'-

dichlorophenylthio)ethylamine (F-49). MS m/z: 359 (M.sup.+).

DETD [1293] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-chloroacetophenone to thereby give (+)-N-(1-(3-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-50). MS m/z: 359 (M.sup.+).

DETD [1294] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-chloroacetophenone to thereby give (+)-N-(1-(4-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-51). MS m/z: 359 (M.sup.+).

DETD [1295] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoroacetophenone to thereby give (+)-N-(1-(3-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-52). MS m/z: 343 (M.sup.+).

DETD [1296] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-fluoroacetophenone to thereby give (+)-N-(1-(4-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-53). MS m/z: 343 (M.sup.+).

DETD [1297] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dimethylacetophenone to thereby give (+)-N-(1-(2,5-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-54). MS m/z: 353 (M.sup.+).

DETD [1298] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dimethylacetophenone to thereby give (+)-N-(1-(2,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-55). MS m/z: 353 (M.sup.+).

DETD [1299] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dichloroacetophenone to thereby give (+)-N-(1-(2,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-57). MS m/z: 395 (M.sup.+).

DETD [1300] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dichloroacetophenone to thereby give (+)-N-(1-(3,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-58). MS m/z: 395 (M.sup.+).

DETD [1301] 3'-Hydroxyacetophenone (200 mg) was dissolved in acetonitrile (4 ml). After adding **ethyl** iodide (0.2 ml) and potassium carbonate (347 mg), the mixture was stirred at 70.degree. C. for 9 hours. After 9 hours, water and **ethyl** acetate were added to the reaction mixture followed by separation. The organic layer was washed with a saturated aqueous solution. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane: **ethyl** acetate=8:1) to thereby give 204 mg of 3'-ethoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-ethoxyacetophenone to thereby give (+)-N-(1-(3-ethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-63). MS m/z: 369 (M.sup.+).

DETD [1302] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-propyl iodide to thereby give 3'-n-propoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-propoxyacetophenone to thereby give (+)-N-(1-(3-n-propoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-64). MS m/z: 383 (M.sup.+).

DETD [1303] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-butyl iodide to thereby give 3'-n-butoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-butoxyacetophenone to thereby give (+)-N-(1-(3-n-butoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-65). MS m/z: 397 (M.sup.+).

DETD [1304] The procedure employed for the synthesis of 3'-ethoxyacetophenone

was repeated but replacing the **ethyl** iodide by n-hexyl bromide to thereby give 3'-n-hexyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-hexyloxyacetophenone to thereby give (.-.)-N-(1-(3-n-hexyloxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2255). MS m/z: 425 (M.sup.+).

DETD [1305] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isopropyl iodide to thereby give 3'-isopropoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isopropoxyacetophenone to thereby give (.-.)-N-(1-(3-isopropoxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-67). MS m/z: 383 (M.sup.+).

DETD [1306] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by dodecane iodide to thereby give 3'-dodecylxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-dodecyloxyacetophenone to thereby give (.-.)-N-(1-(3-n-dodecyloxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-68). MS m/z: 509 (M.sup.+).

DETD [1307] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isobutyl iodide to thereby give 3'-isobutoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isobutoxyacetophenone to thereby give (.-.)-N-(1-(3-isobutoxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-69). MS m/z: 397 (M.sup.+).

DETD [1308] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-chlorobenzyl bromide to thereby give 3'-(4-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-chlorobenzoyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(4-chlorobenzoyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2258). MS m/z: 465 (M.sup.+).

DETD [1309] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-chlorobenzyl bromide to thereby give 3'-(2-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chlorobenzoyloxy)acetophenone to thereby give (+)-N-(1-(3-(2-chlorobenzoyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-71). MS m/z: 465 (M.sup.+).

DETD [1310] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by benzyl bromide to thereby give 3'-benzyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-benzyloxyacetophenone to thereby give (.-.)-N-(1-(3-benzyloxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-72). MS m/z: 431 (M.sup.+).

DETD [1311] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2,6-dichlorobenzyl bromide to thereby give 3'-(2,6-dichlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2,6-dichlorobenzoyloxy)acetophenone to thereby give (+)-N-(1-(3-(2,6-dichlorobenzoyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-73). MS m/z: 501 (M.sup.+).

DETD [1312] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(6-chlorohexyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by

3'-(6-chlorohexyloxy)acetophenone to thereby give (+-)-N-(1-(3-(6-chlorohexyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2260).

- DETD [1314] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(2-chloroethoxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chloroethoxy)acetophenone to thereby give (+-)-N-(1-(3-(2-chloroethoxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-75). MS m/z: 403 (M.sup.+).
- DETD [1315] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-methylbenzyl bromide to thereby give 3'-(2-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-methylbenzyl)acetophenone to thereby give (+-)-N-(1-(3-(2-methylbenzyl) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio) ethylamine (F-76). MS m/z: 445 (M.sup.+).
- DETD [1316] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-methylbenzyl bromide to thereby give 3'-(4-methylbenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-methylbenzyloxy)acetophenone to thereby give (+-)-N-(1-(3-(4-methylbenzyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2268). MS m/z: 445 (M.sup.+).
- DETD [1317] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylfuran to thereby give (+-)-N-(1-(2-(5-methyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-78). MS m/z: 329 (M.sup.+).
- DETD . . . The procedure employed for the synthesis of F-I 2 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylfuran to thereby give (+-)-N-(1-(2-furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-79). MS m/z: 315 (M.sup.+).
- DETD [1319] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-1-methylpyrrole to thereby give (+)-N-(1-(2-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio) ethylamine (F-80). MS m/z: 328 (M.sup.+).
- DETD [1320] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (+)-N-(1-(2-thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-81). MS m/z: 331 (M.sup.+).
- DETD [1321] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2,5-dimethylfuran to thereby give (+-)-N-(1-(3-(2,5-dimethyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-82). MS m/z: 343 (M.sup.+).
- DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylthiophene to thereby give (+)-N-(1-(3-thienyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-83). MS m/z: 331 (M.sup.+).
- DETD [1323] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylthiophene to thereby give (+-)-N-(1-(2-(5-methyl)thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-84). MS m/z: 345 (M+).
- DETD . . . procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-1-methylpyrrole to thereby give (+)-N-(1-(3-(1-methyl) pyrrolyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-85). MS m/z: 329 (M.sup.+).
- DETD [1325] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 5-acetyl-2,4-dimethylthiazole to thereby give (+-)-N-(1-(5-(2,4-dimethyl)thiazolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-86). MS m/z: 360 (M.sup.+).
- DETD [1326] The procedure employed for the synthesis of 3'-ethoxyacetophenone

was repeated but replacing the **ethyl** iodide by cyclohexylmethyl bromide to thereby give 3'-(cyclohexylmethoxybenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(cyclohexylmethoxybenzyloxy)-acetophenone to thereby give (.-.-)-N-(1-(3-(cyclohexylmethoxybenzyloxy) phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-90). MS m/z: 437 (M.sup.+).

DETD [1327] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyridine to thereby give (.-.-)-N-(1-(2-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-91). MS m/z: 327 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylpyridine to thereby give (.-.-)-N-(1-(3-pyridyl) **ethyl**)-2-(2',5'-dichlorophenylthio) ethylamine (F-92). MS m/z: 326 (M.sup.+)

DETD [1329] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4-acetylpyridine to thereby give (.-.-)-N-(1-(4-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-93). MS m/z: 326 (M.sup.+).

DETD [1330] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyrazine to thereby give (.-.-)-N-(1-(2-pyrazyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-94). MS m/z: 327 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2-(methylaminesulfonyl)thiophene to thereby give (.-.-)-N-(1-(3-(2-methylaminosulfonyl)thienyl) **ethyl**)-2-(2',5'-dichlorophenylthio) ethylamine (F-95). MS m/z: 425 (M.sup.+).

DETD [1332] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylindole to thereby give (.-.-)-N-(1-(3-indolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-96). MS m/z: 364 (M.sup.+).

DETD . . . was heated under reflux for 30 minutes. Then it was brought back to room temperature and separated into aqueous and **ethyl** acetate layers. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=3:1) to thereby give 510 mg of a bromo compound. This bromo compound (500 mg) was dissolved in acetonitrile (10 ml) and potassium carbonate (763 mg) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.18 ml) was added thereto. After further adding tetrabutylammonium iodide (41 mg), the mixture was heated under reflux. After 2. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=2:1) to thereby give 280 mg of a F-97. MS m/z: 544 (M+1.sup.+).

DETD [1348] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-111. MS m/z: 587 (M+1.sup.+).

DETD [1349] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-112. MS m/z: 601 (M+1.sup.+).

DETD [1350] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-113. MS m/z: 544 (M.sup.+).

DETD [1351] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-114. MS m/z: 628 (M.sup.+).

DETD [1352] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-115. MS m/z: 572 (M.sup.+).

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=363.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=377.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=405.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=419.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=433.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-a-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=447.

DETD . . . synthesized by almost the same method as the one employed for the synthesis of K-2310 but replacing the 4-methy benzy **amine** and 4-(trifluoromethoxy)benzaldehyde respectively by 4-(trifluoromethyl)benzylamine and 3,4-dimethylbenzaldehyde.

CLM What is claimed is:

6. The compound, salt or hydrate of claim 5 wherein Ar.sub.1 is selected from the group consisting of phenyl, **naphthyl**, indolyl, fluorenyl, dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl, pyridin-4-yl, quinolin-2-yl and dibenzylamino.

8. The compound, salt or hydrate of claim 7 wherein Ar.sub.2 is selected from the group consisting of phenyl, **naphthyl**, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl.

. . . of claim 6 or 7 wherein Ar.sub.2 is selected from the group consisting of optionally substituted phenyl and optionally substituted **naphthyl**.

. . . hydrate of claim 11 wherein p is 1 and Ar.sub.2 is selected from the group consisting of 3-methoxyphenyl and unsubstituted **naphthyl**.

14. The compound, salt or hydrate of claim 11 wherein p is 0, Ar.sub.2

is 3-methoxyphenyl or unsubstituted **naphthyl**, and q is an integer of from 1 to 8, inclusive.

- . . . halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted **naphthyl**; Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the . . . one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted **naphthyl**; R.sup.14 is selected from the group consisting of unsubstituted lower alkyl and lower alkyl substituted with one or more halogens; . . .
- . . . halogens, halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and unsubstituted **naphthyl**; Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from the . . . with one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and unsubstituted **naphthyl**; r is 0 or 1, wherein when r is 1, R.sup.12 is hydrogen.
- . . . alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens; Ar.sub.6 is 3-methoxyphenyl or a-**naphthyl**; and u is an integer of from 2 to 6, inclusive.
- . . . alkoxy, lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens; Ar.sub.6 is **naphthyl** or methoxyphenyl; t is zero; u is an integer of from 0 to 8, inclusive; W is carbonyl; and R.sup.17. . .
- . . . alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens; Ar.sub.6 is 3-methoxyphenyl or c-**naphthyl**; and u is 1.

36. (R)-N-[1-(1'-**naphthyl**)ethyl]-2-(2',5'-dichlorophenylthio)ethylamine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(5-[[4-(trifluoromethoxy)phenyl]thio]pentyl)amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[[4-(trifluoromethoxy)phenyl]thio]butyl)amine, N-{4-[(2,4-dimethylphenyl)thio]butyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(5-[[4-(trifluoromethyl)phenyl]thio]pentyl)amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[(2,4,5-trichlorophenyl)thio]butyl)amine, N-{5-[(4-chlorophenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-{5-[(2,4-dimethylphenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-1(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[[4-(trifluoromethyl)phenyl]thio]butyl)amine, N-(4-[(4-methylphenyl)thio]butyl)-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-(4-[(4-chlorophenyl)thio]butyl)-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(6-[[4-(trifluoromethoxy)phenyl]thio]hexyl)amine, N-{5-[(4-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-{5-[(2,4,5-trichlorophenyl)thio]pentyl}amine, N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]butyl)amine, N-{5-[(2,5-dichlorophenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine, N-{5-[(4-fluorophenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine,

N-{6-[(4-chlorophenyl)thio]hexyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{4-[(3-methoxyphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine,
 N-5-[(4-methylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{4-[(2,5-dichlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine,
 N-[(1R)-1-(1-naphthyl)ethyl]-N-{5-[(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thio]pentyl}amine,
 N-[(1R)-1-(1-naphthyl)ethyl]-N-{7-[(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thio]heptyl}amine,
 N-{4-[5-ethoxy-1,3-benzothiazol-2-yl]thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-{[5-(3-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N-[(1R)-1-(1-naphthyl)ethyl]-N-{3-[(4-(trifluoromethyl)phenyl)thio]propyl}amine,
 N-[(1R)-1-(1-naphthyl)ethyl]-N-{4-[(3-(trifluoromethyl)phenyl)thio]butyl}amine, N-{4-[(4-fluorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine, N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1,N1-di(4-methylbenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1,N1-di[4-(trifluoromethoxy)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(4-chlorobenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1,N1-di[4-(trifluoromethyl)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1,N1-di(4-chlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1,N1-di(4-chlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1,N1-di(4-methoxybenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-benzyl-N1-(3,4-dichlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, N1-benzyl-N1-(4-chlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide,
 N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, or
 N1,N1-di(3,4-dichlorobenzyl)-3-[[[(1R)-1-(1-naphthyl)ethyl]amino]propanamide, or a salt or hydrate thereof.

49. A method for treating or preventing a disorder selected from the group consisting of hyperparathyroidism, renal osteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering to a patient suffering from said disorder a therapeutically effective amount of said compound. . .
 56. A pharmaceutical composition for treatment of **osteoporosis** comprising the compound, salt or hydrate claimed in any one of claims

L2 ANSWER 9 OF 26 USPATFULL on STN
 AN 2002:186297 USPATFULL
 TI **Calcilytic** compounds
 IN Del Mar, Eric G., Salt Lake City, UT, UNITED STATES
 Barmore, Robert M., Salt Lake City, UT, UNITED STATES
 Sheehan, Derek, Salt Lake City, UT, UNITED STATES
 Van Wagenen, Bradford C., Salt Lake City, UT, UNITED STATES
 Callahan, James F., Philadelphia, PA, UNITED STATES
 Keenan, Richard M., Malvern, PA, UNITED STATES
 Kotecha, Nikesh R., Thurmaston, UNITED KINGDOM
 Lago, Maria Amparo, Audobon, PA, UNITED STATES
 Southall, Linda Sue, West Chester, PA, UNITED STATES
 Thompson, Mervyn, The Pinnacles, UNITED KINGDOM
 PA NPS Pharmaceuticals, Inc. (U.S. corporation)
 PI US 2002099220 A1 20020725
 AI US 2001-33001 A1 20011019 (10)
 RLI Division of Ser. No. US 1998-132179, filed on 11 Aug 1998, PENDING
 Continuation-in-part of Ser. No. US 1996-629608, filed on 9 Apr 1996,
 ABANDONED
 PRAI US 1996-32263P 19961203 (60)
 DT Utility
 FS APPLICATION
 LREP Richard San Pietro, FOLEY & LARDNER, P.O. Box 80278, San Diego, CA,
 92138-0278
 CLMN Number of Claims: 31
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 3048
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
 receptor activity. Also described are the use of **calcilytic**
 compounds to inhibit calcium receptor activity and/or achieve a
 beneficial effect in a patient; and techniques which can be used to
 obtain additional **calcilytic** compounds.
 TI **Calcilytic** compounds
 AB The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
 receptor activity. Also described are the use of **calcilytic**
 compounds to inhibit calcium receptor activity and/or achieve a
 beneficial effect in a patient; and techniques which can be used to
 obtain additional **calcilytic** compounds.
 SUMM . . . Number WO 94/18959, and Nemeth et al., PCT/US94/12117,
 International Publication Number WO 95/11211, feature calcium
 receptor-active molecules and refer to **calcilytics** as
 compounds able to inhibit calcium receptor activity. For example, WO
 94/18959 on page 8, lines 2-13 asserts:
 SUMM . . . can be identified and used as lead molecules in the discovery,
 development, design, modification and/or construction of useful
 calcimimetics or **calcilytics** which are active at Ca_{sup}.2+
 receptors.
 SUMM [0011] Such calcimimetics or **calcilytics** are useful in the
 treatment of various disease states characterized by abnormal levels of
 one or more components, e.g., polypeptides. . .
 SUMM [0013] The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
 receptor activity. The ability of a compound to "inhibit calcium
 receptor activity". . .
 SUMM [0014] The use of **calcilytic** compounds to inhibit calcium

receptor activity and/or achieve a beneficial effect in a patient are described below. Also described below are techniques which can be used to obtain additional **calcilytic** compounds.

SUMM [0015] An example of featured **calcilytic** compounds are Structure I .alpha., -disubstituted arylalkylamine derivatives having the chemical formula:

SUMM [0028] Preferred **calcilytic** compounds have an IC.sub.50.ltoreq.50 .mu.M, more preferably an IC.sub.50<10 .mu.M, and even more preferably an IC.sub.50<1 .mu.M, as measured using. . .

SUMM [0032] Patients benefiting from the administration of a therapeutic amount of a **calcilytic** compound can be identified using standard techniques known to those in the medical profession. Diseases or disorders which can be. . .

SUMM [0035] Preferably, the **calcilytic** compounds are used to treat diseases or disorders selected from the group consisting of: hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

SUMM . . . invention describes a method of treating a patient comprising the step of administering to the patient an amount of a **calcilytic** compound sufficient to increase serum PTH level. Preferably, the method is carried out by administering an amount of the compound. . .

SUMM [0041] Another aspect of the present invention features Structure I **calcilytic** compounds.

SUMM [0042] Another aspect of the present invention features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a **calcilytic** compound described herein. The pharmaceutical composition contains the **calcilytic** compound in a form suitable for administration into a mammal, preferably, a human being. Preferably, the pharmaceutical composition contains an amount of a **calcilytic** compound in a proper pharmaceutical dosage form sufficient to exert a therapeutic effect on a human being. However, multiple doses. . .

SUMM . . . or in vitro and is particularly useful to identify those Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives most able to act as **calcilytic** compounds. In vivo assays include measuring a physiological parameter related to calcium receptor activity, such as serum hormone levels or serum calcium ion concentration. In vitro assays include measuring the ability of the **calcilytic** compound to affect intracellular calcium concentration, or cellular hormone secretion. Examples of hormones levels which can be affected by **calcilytic** compounds include PTH and calcitonin.

SUMM [0046] The **calcilytic** compounds described herein can be used as part of in vivo or in vitro methods. Preferably, the compounds are used. . . a patient. Examples of in vitro uses, and other in vivo uses, include use in a method to identify other **calcilytic** compounds and use as a tool to investigate calcium receptor activity or the physiological effects of inhibiting calcium receptor activity. . .

SUMM [0048] The present application demonstrates the ability of **calcilytic** compounds to exert a physiologically relevant effect on a cell by illustrating the ability of such compounds to increase PTH secretion and also identifies a target site for **calcilytic** compounds. The present application is believed to be the first to demonstrate that **calcilytic** compounds can increase PTH secretion.

SUMM [0049] Calcium receptors are present on different cell types and can regulate different responses in different cell types. While the **calcilytic** compounds described herein are believed to act at a calcium receptor through a calcium receptor-activity modulating site, unless otherwise explicitly. . . or any particular mode of action.

Rather, the present application demonstrates that compounds able to inhibit calcium receptor activity, whose **calcilytic** activity can be measured in vivo or in vitro, exert significant physiological effects. For example, the present application demonstrates the ability of different **calcilytic** compounds to prevent Ca.sup.2+ inhibition of PTH and, thereby, result in an increase in PTH release.

SUMM [0051] Preferred **calcilytic** compounds described herein are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. Other aspects of the present.

SUMM [0063] **Calcilytic** activity of a compound can be determined using techniques such as those described in the examples below and those described.

SUMM [0064] **Calcilytic** activity varies depending upon the cell type in which the activity is measured. For example, **calcilytic** compounds possess one or more, and preferably all, of the following characteristics when tested on parathyroid cells in vitro:

SUMM . . . and cycloalk. Preferably, R.sub.1 is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl, optionally substituted longer-length alkyl, optionally substituted longer-length alkenyl or optionally substituted cycloalk.

SUMM [0079] More preferably, R.sub.1 is either an optionally substituted phenyl; an optionally substituted **naphthyl**; an optionally substituted pyridyl; an optionally substituted benzothiopyranyl; an optionally substituted carbazole; unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or monosubstituted.

SUMM . . . Preferably, R.sub.3 and R.sub.4 are each independently a lower alkyl, more preferably, R.sub.3 and R.sub.4 are each independently methyl or **ethyl**;

SUMM [0082] R.sub.5 is aryl. Preferably, R.sub.5 is either optionally substituted **naphthyl** or optionally substituted phenyl. More preferably, R.sub.5 is substituted phenyl having a substituent in the meta or para position and.

SUMM . . . substituted. Preferably, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl.

SUMM . . . an aryl, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, or optionally substituted tetrahydronaphthyl. Preferred, R.sub.1 substituents are each independently selected from the group consisting of: unsubstituted alkyl, unsubstituted alkenyl.

SUMM [0114] More preferred **calcilytic** compounds are Structure I derivatives where R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.6, Z, Y.sub.1 and Y.sub.2 are as described above for.

SUMM [0115] R.sub.5 is either phenyl substituted with one to four independently selected substituents or an optionally substituted **naphthyl** having up to four independently selected substituents. R.sub.5 substituents are provided in Section II, supra., including preferred embodiments. More preferably. . . in a meta or para position, more preferably, the substituent present in a meta or para position is either methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy.

SUMM [0116] The activity of different **calcilytic** compounds was measured using the Calcium Receptor Assay described below. Examples of compounds having an IC.sub.50.ltoreq.50 .mu.M include compounds 1, .

SUMM [0120] R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or. . .

SUMM [0127] R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or para position selected from the group consisting of: methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position;. . .

SUMM [0130] The different **calcilytic** compounds described herein can have different stereochemistry around different groups. In an embodiment of the present invention the Structure I. . .

SUMM [0132] The **calcilytic** compounds described herein can be formulated as a pharmaceutical composition to facilitate the administration of the compound to a patient. Preferred formulations contain a pharmaceutically acceptable carrier and a **calcilytic** compound as described in Section II, supra., including the different embodiments.

SUMM . . . effects to patients suffering from a variety of diseases or disorders. Diseases or disorders which can be treated using a **calcilytic** compound are known in the art and can be identified using the present application as a guide. For example, diseases. . .

SUMM [0136] Diseases and disorders which can be treated using the **calcilytic** compounds described herein include those due to different cellular defects related to calcium receptor activity in different cells, such as. . .

SUMM [0142] While **calcilytic** compounds of the present invention will typically be used to treat human patients, they may also be used to treat. . .

SUMM [0143] Preferably, **calcilytic** compounds are used in the treatment of bone and mineral-related diseases or disorders. Bone and mineral-related diseases or disorders comprise. . . and mineral-related diseases or disorders include osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**. More preferably, **calcilytic** compounds are used to treat **osteoporosis**, a disease characterized by reduced bone density and an increased susceptibility to fractures. **Osteoporosis** is associated with aging, especially in women.

SUMM [0144] One way of treating **osteoporosis** is by altering PTH secretion. PTH can have a catabolic or an anabolic effect on bone. Whether PTH causes a. . .

SUMM [0145] As demonstrated by the Examples provided below, **calcilytic** compounds stimulate secretion of PTH. Such **calcilytic** compounds can be used to increase bone formation in a patient, for example, by intermittent dosing, thus achieving intermittent increases. . .

SUMM [0147] The **calcilytic** compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical. . .

SUMM [0155] The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM [0159] The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into

account factors such as the compound IC.sub.50, EC.sub.50, . . .

DETD [0161] This example illustrates the use of the Calcium Receptor Inhibitor Assay. **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

DETD [0170] 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

DETD [0173] Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives include compounds which have both **calcilytic** activity and .beta.-adrenergic receptor activity. If desired, .beta.-adrenergic activity can be reduced using appropriate functional groups and structural modifications. Modifications. . .

DETD [0174] In one embodiment of the present invention the **calcilytic** compounds have an IC.sub.50.gtoreq.1.0 .mu.M, at the .beta.-adrenergic receptor as measured using the ".beta.-Adrenergic Receptor Binding Assay" described below. In other embodiments, using the .beta.-Adrenergic Receptor Assay **calcilytic** compounds have an IC.sub.50.gtoreq.1.0 .mu.M, and IC.sub.50.gtoreq.10.0 .mu.M.

DETD [0177] This example illustrates the ability of different **calcilytic** compounds to exert a biological effect on PTH secretion. PTH secretion was determined using dissociated bovine parathyroid cells as described. . .

DETD General Procedures for the Preparation of **Calcilytic** Compounds

DETD [0189] The **calcilytic** compounds described by the present invention can be prepared using standard techniques. For example, an overall strategy for preparing preferred. . .

DETD . . . many of the compounds was carried out as follows: A solution of glycidyl ether (i.e., 1,2-epoxy-3-phenoxypropane, 1 mmol) and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, 1.5 mmol) in absolute ethanol (2 mL) is stirred overnight at 50-60.degree. C. The product is purified by. . .

DETD . . . washed with 10% aqueous NaHCO.sub.3 (3.times.200 ml), dried over anhydrous sodium sulfate, filtered, and concentrated. Kugelrohr distillation (.about.100 microns) yielded 1-naphthyl glycidyl ether as a clear, colorless oil: GC/EI-MS, m/z (rel. int.) 200 (M.sup.+, 61), 184 (1), 169 (5), 157 (12), . . .

DETD [0196] A stirred solution of 1-naphthyl glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-fluorophenyl)ethylamine (334 mg, 2 mmol) in absolute ethanol (2 mL) was heated at. . .

DETD . . . mmol) were dissolved in 30 mL of water and enough acetone to maintain solubility at 0.degree. C. A solution of **ethyl** chloroformate (20.1 g, 185 mmol) in acetone (100 mL) was then added dropwise. An aqueous solution (95 mL) of sodium. . .

DETD Preparation of N-[2-Hydroxy-3-(4-chlorophenoxy)-propyl]-1,1-dimethyl-2-(4-methoxyphenylethyl)-**amine** Hydrochloride, Compound 5

DETD Preparation of N-[2-Hydroxy-3-(4-t-butylphenoxy)-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl-amine** Hydrochloride Compound 6

DETD [0220] Using the method of Example 5, supra, 1-naphthyl glycidyl ether (1.0 g, 5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.0 mg, 5.6 mmol) were used to prepare the free base of. . .

DETD Preparation of N-[2-Hydroxy-3-(2-ethyl)hexanoxypropyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine, Compound 28

DETD Resolution of the Enantiomers (R) and (S) 13 N-[2-Hydroxy-3-(2-ethyl)hexanoxypropyl]-1,1dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 63 and 64

DETD [0230] The enantiomers (R) and (S)-N-[2-hydroxy-3-(2-ethyl)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine hydrochloride were prepared using the method of Example 7, supra. GC/EI-MS of each enantiomer gave m/z (rel. int.) 366 (M+1, . . . (21), 115 (11), 100 (4), 71 (21). The hydrochloride salt of each enantiomer was prepared by treatment of the free amine in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

DETD [0234] Using the method of Example 4, supra, 2-naphthyl glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (358 mg, 2 mmol) were used to prepare the free base of. . .

DETD Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 113

DETD . . . washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by preparative TLC using ethyl acetate/hexane as the elutant. The yield of 1-ethyl-1-methyl-2-(4-hydroxyphenyl)-nitroethane was 0.21 grams.

DETD . . . a suspension of 40% (wt/wt) potassium fluoride on alumina (0.73 g, 5 mmol) in 3 mL of acetonitrile were added 1-ethyl-1-methyl-2-(4-hydroxyphenyl)nitroethane (0.21 g, 1.0 mmol) and iodomethane (0.21 g, 1.5 mmol). The reaction was stirred at room temperature for 4 days. . . washed with sodium bisulfite, sodium carbonate, and saturated brine, then dried over anhydrous sodium sulfate and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane was 0.183 g.

DETD . . . 5 mL of methanol, followed by the addition of sodium borohydride (0.05 g, 1.2 mmol). After stirring for 5 minutes, 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane (0.18 g, 0.807 mmol) in 3 mL of methanol was added, and stirred for 5 minutes. Sodium borohydride (0.11 g, . . . hydroxide. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine was 0.127 grams.

DETD [0332] Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.086 g, 0.57 mmol) and 1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine (0.11 g, 0.57 mmol) were used to prepare 90 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD Preparation of N-(2-Hydroxy-3-phenoxypentyl)-1,1-dimethyl-2-(2-naphthyl)ethylamine Hydrochloride, Compound 120

DETD [0354] Using the method of Example 52, supra, 2-amino-methylnaphthalene (2.51 g, 16 mmol) was used to prepare 1.9 g of 1,1-dimethyl-2-(2-naphthyl)ethylamine. 0 Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.163 g, 1.1 mmol) and 1,1-dimethyl-2-(2-naphthyl)ethylamine (0.26 g, 1.3 mmol) were used to prepare 243 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD . . . (230 mg, 1.5 mmol) were used to 10 prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 130 mg of the title. . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 88 mg of a white. . .

DETD Synthesis of (R/S)-1-[[2,2-dimethyl-(4-methoxy)phenethyl]]amino-2-hydroxy-4(1'-naphthyl)-butane, Compound 162

DETD . . . with CH₂Cl₂ and was extracted with sodium sulfite (aqueous) and NaHCO₃ (aqueous), dried over MgSO₄, filtered and evaporated to give 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) that was carried without further purification.

DETD [0387] A solution of 1-[(2-oxoaryl)**ethyl**]-naphthaline (1 g) and 1,1-dimethyl-2-(4-methoxyphenyl) ethylamine (985 mg, 5.5 mmol) in ethanol (25 mL) was heated at reflux for 12 hours.. . . addition of ether, crystals formed and were subsequently collected and dried in a vacuum oven to give 1.4 g of (R/S)-1-]]2,2-dimethyl-(4'methoxy)-phenethyl]]amino-2-hydroxy-4(1'-**naphthyl**)-butane. ESMS [(M+H).sup.+ = 378, .sup.1H NMR (CDCl.sub.3, 360 MHz) @300.degree. K. .delta. 8.06 (1H, d of d), 7.83 (1H, d of d),. . .

DETD N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)**ethyl**]amine
Hydrochloride Salt Compound 165

DETD [0400] e) N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)**ethyl**]amine hydrochloride salt.

DETD [0419] Compound 92: N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(1-**naphthyl**)ethylamine.

CLM What is claimed is:

- . . . and N(lower alk).sub.2, R.sub.3 and R.sub.4 is each independently lower alk or together cyclopropyl; R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least. . .
- . . . any of claims 1-2, wherein R.sub.2 is OH or methoxy, R.sub.6 is hydrogen, R.sub.3 or R.sub.4 is independently methyl or **ethyl**; and Z is O, S, or unsubstituted alkylene.
- . . . 5. The compound of claims 1-2, wherein R.sub.2 is hydrogen, R.sub.6 is hydrogen, R.sub.3 and R.sub.4 is independently methyl or **ethyl**; and Z is O or methylene.
- . . . selected from the group consisting of: osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

10. The method of claim 9, wherein disease or disorder is **osteoporosis**.

23. The method of claim 9 or 13, wherein R.sub.5 is an optionally substituted **naphthyl**.

24. The method of claim 23, wherein R.sub.5 is a substituted **naphthyl** having one to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-unsubstituted alkyl, lower-haloalkoxy, unsubstituted alkyl,. . .

25. The method of claim 24, wherein R.sub.5 is **naphthyl**.

28. The method of claim 27, wherein R.sub.3 is methyl or **ethyl**; and R.sub.4 is methyl or **ethyl**.

30. A method of screening for a **calcilytic** compound comprising the step of measuring the ability of a compound to inhibit one or more calcium receptor activities, said. . .

L2 ANSWER 10 OF 26 USPATFULL on STN
AN 2002:168247 USPATFULL
TI **Calcilytic** compounds
IN Lago, Amparo Maria, Audubon, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6417215 B1 20020709
WO 2000045816 20000810

AI US 2001-890310 20010726 (9)
 WO 2000-US2676 20000202
 20010706 PCT 371 date

PRAI US 1999-118240P 19990202 (60)
 DT Utility
 FS GRANTED

EXNAM Primary Examiner: Higel, Floyd D.; Assistant Examiner: Sackey, Ebenezer
 LREP Simon, Soma G., King, William T., Kinzig, Charles M.
 CLMN Number of Claims: 12
 ECL Exemplary Claim: 1
 DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
 LN.CNT 1367

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel **calcilytic** compounds are provided.
 TI **Calcilytic** compounds
 AB Novel **calcilytic** compounds are provided.
 SUMM The present invention relates to novel **calcilytic** compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.

SUMM Various compounds are known to mimic the effects of extra-cellular Ca.sup.2+ on a calcium receptor molecule. **Calcilytics** are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM Ar is phenyl or **naphthyl**, unsubstituted or substituted, heteroaryl or fused heteroaryl, such that the hetero-ring may contain N, O or S and may be. . .

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[[**ethyl**]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM 4'-Cyano-3'-{(R)-3-[1,1-dimethyl-2-(4-**ethyl**-phenyl)-ethylamino]-2-hydroxy-propoxy}-biphenyl-4-carb

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-biphenyl-4carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,6-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-biphenyl-4-carboxylic acid

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[[**ethyl**]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM 4'-Cyano-3'-{(R)-3-[1,1-dimethyl-2-(4-**ethyl** -phenyl)-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carb

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,6-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[1,1-dimethyl-2-(4-**ethyl** -phenyl)-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carb

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,6-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM 4'-Cyano-3'-{(R)-3-[2-(4-**ethyl**-2,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-biphenyl-4-carboxylic acid

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[[**ethyl**]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride;

SUMM . . . in Scheme 2, the formyl biphenyl analog 4 could them be oxidized under standard conditions and transformed to the corresponding **ethyl** ester 5. A solution an aryl alcohol such 1-Scheme 1 or 5-Scheme 2 in acetone is treated with K.sub.2CO.sub.3 heated. . .

SUMM A solution of a glycidyl ether such as 2-Scheme 1, and excess **amine** (typically 1,1-dimethyl-2-(2-**naphthyl**)ethylamine) in absolute ethanol (2 mL), acetonitrile, THF or any other similar solvent in the presence of a suitable. . .

SUMM The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .

SUMM . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.

SUMM **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

SUMM 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a

control) for 90 seconds before increasing the concentration of extracellular Ca.^{sup.2+} from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.^{sup.2+} elicited. . .

SUMM A typical reaction mixture contains 2 nM .^{sup.3H} compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-naphthyl)ethylamine), or .^{sup.3H} compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume. . .

DETD b) **Ethyl**-4-[[3-hydroxyl-4-cyano]phenyl]benzoate

DETD c) **Ethyl**-4-[[3-[[R-glycidyl]oxyl]methyl-4-cyano]phenyl]benzoate

DETD b) **Ethyl**-2-[[3-hydroxyl-4-cyano]phenyl]benzoate

DETD c) **Ethyl**-2-[[3-[[R-glycidyl]oxyl]methyl-4-cyano]phenyl]benzoate

CLM What is claimed is:

. . . or R.sub.1 and R.sub.1' together form a 3 to 7 membered optionally substituted heterocyclic ring; and Ar is phenyl or **naphthyl**, heteroaryl or fused heteroaryl, substituted or unsubstituted, such that the hetero-ring may contain N, O or S and may be. . .

3. A compound according to claim 1 wherein when a phenyl or **naphthyl** moiety is substituted, its substituents are selected from the group consisting of OH, halo, CO.sub.2R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6. . .

5. A compound according to claim 1 selected from the group consisting of: N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-5-[[4-carboxy]phenyl]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-5-[2-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[4-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[2-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[3-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[3-[hydroxymethyl]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[2-hydroxymethylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[3-[**ethyl**]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-4-[3-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; and N-[2R-Hydroxy-3-[2-cyano-4-(2-carboxyphenyl)phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride.

6. A compound according to claim 5 selected from the group consisting of: N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-5-[[4-carboxylphenyl]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[4-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; and N-[2R-Hydroxy-3-[[2-cyano-4-[3-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride.

yl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[2-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[3-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[hydroxymethyl]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[2-hydroxymethylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[[ethyl]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-4-[3-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; and N-[2R-Hydroxy-3-[2-cyano-4-(2-carboxyphenyl)phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride.

7. A compound according to claim 6 selected from the group consisting of: N-[2R-Hydroxy-3-[2-cyano-5-[2-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-5-[4-carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-5-[4-carboxy]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[4-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[carbetoxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[2-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[3-formylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[hydroxymethyl]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[2-hydroxymethylphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[[2-cyano-4-[[3-[[ethyl]carboxyl]]phenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; N-[2R-Hydroxy-3-[2-cyano-4-[3-carboxyphenyl]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride; and N-[2R-Hydroxy-3-[2-cyano-4-(2-carboxyphenyl)phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine hydrochloride.

11. A method according to claim 10 wherein the bone or mineral homeostasis disease or disorder is **osteoporosis**.

L2 ANSWER 11 OF 26 USPATFULL on STN
 AN 2002:122786 USPATFULL
 TI **Calcilytic** compounds
 IN Bhatnagar, Pradip Kumar, Exton, PA, United States
 Burgess, Joelle Lorraine, Phoenixville, PA, United States
 Callahan, James Francis, Philadelphia, PA, United States
 Calvo, Raul Rolando, Royersford, PA, United States
 Del Mar, Eric G., Salt Lake City, UT, United States
 Lago, Maria Amparo, Audubon, PA, United States
 Nguyen, Thomas The, King of Prussia, PA, United States
 PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
 NPS Pharmaceuticals, Salt Lake City, UT, United States (U.S. corporation)
 PI US 6395919 B1 20020528
 WO 9951569 19991014
 AI US 2000-647793 20001005 (9)

WO 1999-US7722

19990408

20001005 PCT 371 date

PRAI US 1998-81093P

19980408 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Higel, Floyd D.; Assistant Examiner: Sackey, Ebenezer

LREP Simon, Soma G., King, William T., Kinzig, Charles M.

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 2112

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel **calcilytic** compounds, pharmaceuticals compositions
cotaining said compounds and their use as calcium receptor antagonists.

TI **Calcilytic** compounds

AB Novel **calcilytic** compounds, pharmaceuticals compositions
cotaining said compounds and their use as calcium receptor antagonists.

SUMM The present invention relates to novel **calcilytic** compounds,
pharmaceutical compositions containing these compounds and their use as
calcium receptor antagonists.

SUMM Various compounds are known to mimic the effects of extra-cellular
Ca.sup.2+ on a calcium receptor molecule. **Calcilytics** are
compounds able to inhibit calcium receptor activity, thereby causing a
decrease in one or more calcium receptor activities evoked by
extracellular Ca.sup.2+. **Calcilytics** are useful as lead
molecules in the discovery, development, design, modification and/or
construction of useful calcium modulators which are active at Ca.sup.2+
receptors. Such **calcilytics** are useful in the treatment of
various disease states characterized by abnormal levels of one or more
components, e.g., polypeptides. . . secretion of which is regulated
or affected by activity at one or more Ca.sup.2+ receptors. Target
diseases or disorders for **calcilytic** compounds include
diseases involving abnormal bone and mineral homeostasis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture
healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral
hypercalcemia associated with malignancy and fracture healing, and
osteoporosis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture
healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral
hypercalcemia associated with malignancy and fracture healing, and
osteoporosis.

SUMM R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or,
together, form cyclopropyl;

SUMM R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or,
together, form cyclopropyl;

SUMM Most preferably, R.sub.5 is phenyl, **naphthyl**, heteroaryl or
fused heteroaryl, wherein the heteroring contains N, O or S, and is
aromatic, dihydro or tetrahydro; unsubstituted or. . .

SUMM . . . systems. Aryl includes carbocyclic aryl, and biaryl groups, all
of which may be optionally substituted. Preferred aryl include phenyl
and **naphthyl**. More preferred aryl include phenyl. Preferred
substituents are selected from the group consisting of halogen,
C.sub.1-4 alkyl, OCF.sub.3, CF.sub.3, OMe, . . .

SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;

SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;

SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;

SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;

SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-

dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carbethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carbethoxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carbethoxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-
 ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**
)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-
 1,1-dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-
 methoxycarbonylmethyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-
 carboxymethyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(3-
 hydroxy)propyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-
 methoxyphenyl)ethylamino]-3-[(4-(2-hydroxy)**ethyl**
)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-
 methoxyphenyl)ethylamino]-3-[(4-(2-cyano)**ethyl**
)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-
 methoxycarbonyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-
 carboxy)phenoxy]-propan-2-ol;
 SUMM N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl-2-
 [phthalimido]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**
]ethylamine;
 SUMM N-[2R-hydroxy-3-[[2-nitro-4-[2S-carboxy-2-[[[2-
 carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-
 dimethyl-2-[**naphthyl**]ethylamine;
 SUMM N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl-2-[[[2-
 carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-
 dimethyl-2-[**naphthyl**]ethylamine;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-
 aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-
 aminophenoxy)-4-carboxy)phenoxy]-propan-2-ol;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-

dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-
 5-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**
)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carbethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carbethoxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carbethoxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-
 ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**
)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-
 1,1-dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-
 aminophenoxy)4-methoxycarbonyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-
 methoxycarbonylmethyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-
 carboxymethyl)phenoxy]-propan-2-ol;
 SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-
 methoxycarbonyl)phenoxy]-propan-2-ol; N-[2R-hydroxy-3-[[2-nitro-4-[2S-
 ethoxycarbonyl-2-[methylsulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-[4-
 methoxyphenyl]ethylamine; N-[2R-hydroxy-3-[[2-nitro-4-[2S-
 methoxycarbonyl-2-[phthalimido]phenoxy]propyl]-1,1-dimethyl-2-[
naphthyl]ethylamine;
 SUMM N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl-2-[[[2-
 carboxy]phenyl]carbonyllamino]**ethyl**]phenoxy]propyl]-1,1-
 dimethyl-2-[**naphthyl**]ethylamine; and
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboxyethyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-
 dimethyl-2-(2-**naphthyl**)ethylamine;
 SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-

dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carbethoxyethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carboxyethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carbethoxymethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboxymethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carbethoxymethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-
dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-
ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**
)ethylamine;
SUMM (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-
1,1-dimethyl-2-(2-**naphthyl**)ethylamine;
SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-
aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol; and
SUMM . . . was used. This method can also be used for aryl alcohols. A
solution of the substituted glycidyl ether and excess **amine**
(typically 1,1-dimethyl-2-(4-methyloxyphenyl)ethylamine) in absolute
ethanol, acetonitrile, THF or any other similar solvent in the presence
of a suitable catalyst such. . .
SUMM The **calcilytic** compounds can be administered by different
routes including intravenous, intraperitoneal, subcutaneous,
intramuscular, oral, topical (transdermal), or transmucosal
administration. For systemic. . .
SUMM The amounts of various **calcilytic** compounds to be administered
can be determined by standard procedures taking into account factors
such as the compound IC.sub.50, EC.sub.50,. . .
SUMM . . . helpful in treating diseases such as hypoparathyroidism,
osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid
arthritis, Paget's disease, humoral hypercalcemia malignancy and
osteoporosis.
SUMM **Calcilytic** activity was measured by determining the IC.sub.50
of the test compound for blocking increases of intracellular Ca.sup.2+
elicited by extracellular. . .
SUMM 7. To determine the potential **calcilytic** activity of test
compounds, cells were incubated with test compound (or vehicle as a
control) for 90 seconds before increasing the concentration of
extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds
were detected by their ability to block, in a concentration-dependent
manner, increases in the concentration of intracellular Ca.sup.2+
elicited. . .
SUMM A typical reaction mixture contains 2 nM .sup.3H compound
((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-**naphthyl**
)ethylamine), or .sup.3H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-
cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug
membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH
in a reaction volume. . .
DETD a) (R) 4-(2-Phenyl-2-R,S-(methoxycarbonyl)**ethyl**
)-phenoxyglycidol
DETD Preparation of (R)-1-[1,1-Dimethyl-2-(2-**naphthyl**
)ethylamino]-3-[(3-benzyl-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol
Hydrochloride Salt
DETD Preparation of (R)-1-[1,1-Dimethyl-2-(2-**naphthyl**
)ethylamino]-3-[(3-benzyl-4-carboxymethyl)phenoxy]-propan-2-ol
Hydrochloride Salt

DETD Preparation of (R)-1-[1,1-Dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(2-hydroxy)**ethyl**)phenoxy]-2-propan-2-ol Hydrochloride Salt

DETD Preparation of (R)-1-[1,1-Dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(2-cyano)**ethyl**)phenoxy]-propan-2-ol Hydrochloride Salt

DETD . . . and added 4M HCl, concentrated and triturated in ether to give the title compound (0.060 g) with minor impurity of **ethyl** ester. ESMS (M+H).sup.+ m/e 402.2 & 416.4.

DETD . . . (0.25 mL) at reflux for 16 h. The mixture was cooled, evaporated, taken up in 5% NaHCO.sub.3 and extracted into **ethyl** ether. A mixture of this crude compound (0.512 g, 2.43 mmol), K.sub.2CO.sub.3 (1.0 g, 7.27 mmol) and 2R-(-)-glycidyl-3-nitrobenzenesulfonate (0.630 g, . . .

DETD . . . concentrated and triturated in ether to give a white powder of the title compound (0.067 g) with minor impurity of **ethyl** ester. ESMS (M+H).sup.+ m/e 447.2 & 461.2.

DETD (b) (R)-1-[1,1-Dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-methoxycarbonyl)phenoxy]-propan-2-ol Hydrochloride Salt

DETD Preparation of (R)-1-[1,1-Dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-carboxy)phenoxy]-propan-2-ol Hydrochloride Salt

DETD (a) **Ethyl** (2-Cyano-4-oxyacetyl)phenylacetate

DETD A solution of **ethyl**-4-hydroxyphenylacetate (2.34 g, 13 mmol), SnCl.sub.4 (0.15 mL, 1.3 mmol) and tributylamine (1.2 mL, 5.2 mmol) in toluene (100 mL) was. . .

DETD (b) (2R)-Glycidyl-[**ethyl**-2-cyano-4-hydroxyphenyl]acetate

DETD A solution of **ethyl**-(2-cyano-4-hydroxyphenyl)acetate (0.5 g, 2 mmol) in EtOH/water (1:1, 10 mL) was treated with K.sub.2CO.sub.3 (0.28 g, 2 mmol). After 3 h. . .

DETD A mixture of (2R)-glycidyl-(**ethyl**-2-cyano-4-hydroxyphenyl)acetate 0.2 g, 0.77 mmol), and 4-methoxyphenyl-1,1-dimethylethylamine (0.138 g, 0.77 mmol) in ethanol (20 mL) was heated at reflux for 24. . .

DETD A mixture of (2R)-glycidyl-(**ethyl**-4-hydroxyphenyl)acetate (0.2 g, 0.85 mmol), and 4-methoxyphenyl-1,1-dimethylethylamine (0.15 g, 0.85 mmol) in ethanol (20 mL) was heated at reflux for 24. . .

DETD Preparation of N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl]-2-[phthalimido]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine Hydrochloride

DETD (c) N-[2R-Hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl]-2-[phthalimido]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine Hydrochloride

DETD Preparation of N-[2R-Hydroxy-3-[[2-nitro-4-[2S-carboxy-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine

DETD (a) N-[2R-Hydroxy-3-[[2-nitro-4-[2S-carboxy-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine

DETD Preparation of N-[2R-Hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl]-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine Hydrochloride

DETD (a) N-[2R-Hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl]-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine Hydrochloride

DETD Preparation of (R)-1-1,1-Dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol Dihydrochloride Salt

DETD (e) (R)-1-[1,1-Dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol dihydrochloride salt

DETD A solution of compound from Example 28(d) (0.10 g, 0.4 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)**ethyl** amine (0.07 g, 0.4 mmol) in EtOH (5 mL) was heated to reflux for 18 hr. Solution was concentrated. Flash chromatography. . .

DETD Preparation of (R)-1-1,1-Dimethyl-2-(2-naphthyl
)ethylamino]-3-[(3-(2-aminophenoxy)-4-carboxy)phenoxy]-propan-2-ol
Dihydrochloride Salt

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-
carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl
)ethylamine

DETD (a) **Ethyl**-3-(2-cyano-4-hydroxyphenyl)propionate

DETD To 25.2 g (0.13 mol) of **ethyl**-3-(4-hydroxy-3-
cyanophenyl)propionate in 300 mL of dry toluene was added under argon
12.4 mL (0.052 mol) of tri-n-butylamine followed by 1.5 mL. . . .

DETD . . . cooled and concentrated to a dark oil which was subjected to
flash column chromatography on silica gel eluting with 90:10 hexane:
ethyl acetate (v/v). There was obtained 5.3 g of product
(18.6%). Further elution with 70:30 hexane:**ethyl** acetate (v/v)
yielded 12 g of starting material.

DETD . . . reaction was stirred under argon at reflux for 18 h. The
reaction was concentrated. The residual oil was dissolved in
ethyl acetate and washed with 1N HCl. The **ethyl**
acetate phase was dried, filtered and concentrated to an oil which was
treated with 100 mL of acetic anhydride and refluxed under argon for 30
min. The reaction was concentrated. The resulting oil was dissolved in
ethyl acetate and washed with water. The **ethyl** acetate
layer was dried, filtered and concentrated to an oil which was dissolved
in 200 mL of ethanol and treated. . . 5 h the mixture was neutralized
with 3N HCl to pH 5 and concentrated. The resulting mixture was
extracted with **ethyl** acetate. The **ethyl** acetate
solution was dried, filtered and concentrated to an oil which solidified
on storage: 9.5 g (97%).

DETD (b) **Ethyl**-3-(2-cyano-4-(R)-glycidyloxyphenyl)propionate

DETD A solution of 7.7 g (0.035 mol) **ethyl**-3-(2-cyano-4-
hydroxyphenyl)propionate and 9.1 g (0.035 mol) of 2-(R)-glycidyl-3-
nitrobenzenesulfonate in 100 mL of dry acetone was treated with 7.6 g
(0.055 mol). . . was cooled and filtered. The filtrate was
concentrated and purified by flash column chromatography on silica gel
eluting with 70:30 hexane:**ethyl** acetate to yield 6 g (62%) of
the epoxide.

DETD (c) (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboethoxyethyl)phenoxy)propyl]-
1,1-dimethyl-2-(2-naphthyl)ethylamine

DETD A solution of 2.69 g (0.0098 mol) of the epoxide and 1.95 g of the
amine (0.098 mol) was refluxed in 75 mL of ethanol under argon
for 18 h. The reaction was concentrated and the residue. . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-
carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl
)ethylamine Sodium Salt

DETD To a stirred solution of 100 mg of the **ethyl** ester (0.21 mmol)
in 5 mL of ethanol was added 1 mL of 1N sodium hydroxide (1 mmol). The
mixture was. . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-
carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl
)ethylamine Hydrochloride

DETD (a) **Ethyl** 4-(4-cyano-3-hydroxyphenyl)butanoate

DETD **Ethyl** 4-(4-cyano-3-t-butoxyphenyl)butanoate (6.8 g, 23.5 mmol)
was dissolved in a mixture of acetonitrile (42 mL) and conc. HCl (3.85
mL) and. . . a silica gel column (5.times.15 cm) in CHCl₃.sub.3 and
eluted with 20% EtOAc in CHCl₃.sub.3 to yield 4.5 g of **ethyl**
4-(4-cyano-3-hydroxyphenyl)butanoate: .sup.1H-NMR (CDCl₃.sub.3) 8.2 (1H,
s), 7.42 (1H, d), 6.95 (1H, s), 6.77 (1H, d), 4.2 (2H, q), 2.63 (2H,. . .

DETD Using the method of example 30(b), vide supra, **ethyl**
4-(4-cyano-3-hydroxyphenyl)butanoate (1.4 g, 6 mmol) and (R)-glycidyl
nosylate (1.48 g, 5.71 mmol) were used to prepare 1.47 g (88%) of. . .

DETD (c) (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-

1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride.

DETD Using the method of example 30(c), supra, (R)-2-cyano-5-(3-carbethoxypropyl)phenyl glycidyl ether (1.47 g, 5.08 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (1.1 g, 5.59 mmol) were used to prepare the title compound as a white solid: .sup.1H-NMR (CDCl.sub.3) .delta. 9.82 (1H, . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Sodium Salt

DETD (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.77 g, 1.58 mmol) was hydrolyzed by stirring overnight at room temperature in 25 mL of EtOH containing 2.37 mmol. . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD (a) **Ethyl** 3-(4-cyano-3-hydroxyphenyl)propionate

DETD . . . (9.0 mL, 15 g, 53 mmol, 1.2 equiv) was added over a period of 5 min to a solution of **ethyl** 3-(4-hydroxy-3-methoxyphenyl)propionate (8.7 mL, 10 g, 45 mmol, 1 equiv) and pyridine (9.0 mL, 8.8 g, 110 mmol, 2.5 equiv) in. . . (200 mm.times.50 mm dia.). The fractions containing only product were combined and concentrated (75.degree. C.). This provided 12.3 g of **ethyl** 3-(4-trifluoromethanesulfoxy-3-methoxyphenyl)propionate as a nearly-colorless oil.

DETD To a mixture of **ethyl** 3-(4-trifluoromethanesulfoxy-3-methoxyphenyl)propionate (11.9 g, 33.4 mmol, 1 equiv) and zinc cyanide (7.8 g, 66.4 mmol, 2.0 equiv) in deoxygenated dry DMF. . . flash silica gel (200 mm.times.50 mm dia.). The fraction containing product was concentrated (75.degree. C.) yielding 4.70 g (60.3%) of **ethyl** 3-(4-cyano-3-methoxyphenyl)propionate as a white crystalline solid.

DETD A mixture of **ethyl** 3-(4-cyano-3-methoxyphenyl)propionate (3.17 g, 13.6 mmol, 1 equiv) and sodium cyanide (2.00 g, 40.8 mmol, 3.00 equiv) in DMSO (60 mL). . . layer was washed with H.sub.2O (2.times.50 mL), dried (anh. Na.sub.2SO.sub.4), and concentrated (75.degree. C.). This yielded 2.05 g (68.8%) of **ethyl** 4-(4-cyano-3-hydroxyphenyl)propionate as a light yellow crystalline solid: .sup.1H-NMR (CDCl.sub.3) 7.42 (1H, d), 7.40 (1H, br s), 6.92 (1H, d), 6.81. . . .

DETD Using the method of example 30(b), supra, **ethyl** 3-(4-cyano-3-hydroxyphenyl)propionate (1.32 g, 6 mmol) and (R)-glycidyl nosylate (1.48 g, 5.71 mmol) were used to prepare 1.35 g (86%) of. . .

DETD (c) (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD Using the method of example 30(c), supra, (R)-2-cyano-5-(2-carbethoxyethyl)phenyl glycidyl ether (1.35 g, 4.9 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (1.07 g, 5.39 mmol) were used to prepare the title compound as a white solid: .sup.1H-NMR (CDCl.sub.3) 9.82 (1H, br. . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxy)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Sodium Salt

DETD (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.54 g, 1.14 mmol) was hydrolyzed by the method of example 34. supra, to give 510 mg of the title. . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD (a) **Ethyl** 4-(3-cyano-4-hydroxyphenyl)butanoate

DETD To an ice cooled solution of **ethyl** 4-(4-

hydroxyphenyl)butanoate (16.73 g, 80.32 mmol) in 200 mL of CHCl₃, was added bromine (4.15 mL, 80.8 mmol). The cooling bath. . . mixture was then washed with water and brine, dried over sodium sulfate and concentrated to give 22.3 g (96.6%) of **ethyl**

4-(3-bromo-4-hydroxyphenyl)butanoate as a crystalline solid.

DETD To a solution of **ethyl** 4-(3-bromo-4-hydroxyphenyl)butanoate (19.8 g, 69 mmol) in 172 mL of N-methyl-2-pyrrolidinone was added CuCN (6.49 g, 72.4 mmol). The solution was. . . then dried over sodium sulfate and concentrated. Purified on silica gel using 60:40 hexanes:EtOAc as the elutant. The yield of **ethyl** 4-(3-cyano-4-hydroxyphenyl)butanoate was 9.84 g (61%): .sup.1H-NMR (CDCl₃.sub.3) 7.67 (1H, s), 7.24-7.29 (2H), 7.94 (1H, d), 4.14 (2H, q), 2.59 (2H, . . .

DETD Using the method of example 30(b), supra, **ethyl** 4-(3-cyano-4-hydroxyphenyl)butanoate (0.93 g, 4 mmol) and (R)-glycidyl nosylate (1.00 g, 3.86 mmol) were used to prepare 0.74 g (66%) of. . .

DETD (c) Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD Using the method of example 30(c), supra, (R)-2-cyano-4-(3-carbethoxypropyl)phenyl glycidyl ether (0.72 g, 2.48 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.52 g, 2.6 mmol) were used to prepare 0.87 g (67%) of the title compound as a white solid: . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Sodium Salt

DETD (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.618 g, 1.17 mmol) was hydrolyzed by the method of example 33, supra, to give 555 mg (90%) of the. . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD (a) Preparation of **Ethyl** 4-(2-cyano-3-hydroxyphenyl)butanoate

DETD Using the method of example 1(a), supra, **ethyl** 4-(2-cyano-3-hydroxyphenyl)butanoate (1.9 g, 7.33 mmol) and (R)-glycidyl nosylate (1.78 g, 7.6 mmol) were used to prepare 1.70 g (80%) of. . .

DETD (c) Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride

DETD Using the method of example 1(b), supra, (R)-2-cyano-3-(3-carbethoxypropyl)phenyl glycidyl ether (0.8 g, 2.77 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.58 g, 2.9 mmol) were used to prepare 1.07 g (74%) of the title compound as a white solid: .sup.1H-NMR. . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Sodium Salt

DETD (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.687 g, 1.3 mmol) was hydrolyzed by the method of example 33, supra, to give 502 mg (80%) of the. . .

DETD (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine

DETD (a) **Ethyl** 3-(2-cyano-4-hydroxyphenyl)propenoate

DETD A solution of 158.1 g (0.8 mol) of 2-cyano-4-bromophenol, 88.11 g (0.88 mol) of **ethyl** methacrylate, 36.5 g (0.12 mol) of tri-o-tolylphosphine and 110.6 g (0.8 mol) of potassium carbonate in 1000 mL of acetonitrile. . . 500 mL of water and the pH adjusted to 3-4 with concentrated hydrochloric acid. The mixture was then extracted with **ethyl** acetate. The **ethyl** acetate solution was

dried over sodium sulfate, filtered and concentrated to approximately 500 mL. The resulting slurry was dissolved in. . .

CLM What is claimed is:

. . or substituted by C.sub.1-4 alkyl or haloalkyl; Y.sub.3 is covalent bond or O; R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or, together, form cyclopropyl; R.sub.5 is aryl or fused aryl, dihydro or tetrahydro fused aryl, unsubstituted or substituted with any. . .

. . to claim 1 having the structure according to Formula (II) hereinbelow: ##STR13## wherein: R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or, together, form cyclopropyl; R.sub.5 is aryl or fused aryl, or dihydro or tetrahydro fused aryl, unsubstituted or substituted with. . .

4. A compound according to claim 3 wherein: R.sub.5 is phenyl, or **naphthyl**, R.sub.6 is H; A and B are, independently, selected from the group consisting of a bond, CH.sub.2, and O, or. . .

5. A compound according to claim 1 selected from the group consisting of: (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-(4-(2-phenyl-2-R,S-methoxycarbonyl)ethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(2-phenyl-2-R,S-carboxyethyl)phenoxy)-propan-2-ol]; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(3-(3-benzyl-4-methoxycarbonylmethyl)phenoxy)-propan-2-ol]; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-benzyl-4-carboxymethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(3-benzyl-4-carboxymethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(3-hydroxy)propyl)phenoxy]-propan-2-ol;

(R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(2-hydroxy)**ethyl**)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-(2-cyano)**ethyl**)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-cyanomethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-cyano)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-nitro-4-cyano)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-nitro-4-(hydroxymethyl)phenoxy)-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-nitro-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-nitro-4-carboxymethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-methoxycarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(4-carboxy)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-cyano-4-ethoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-cyano-4-carboxymethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(4-methoxycarbonyl)ethyl]phenoxy]-propan-2-ol; N-[2R-hydroxy-3-[[2-nitro-4-[2S-ethoxycarbonyl-2-[methylsulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-[4-methoxyphenyl]ethylamine; N-[2R-hydroxy-3-[[2-nitro-4-[2S-carboxy-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine; N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl-2-[[[2-carboxy]phenyl]carbonyl]amino]**ethyl**]phenoxy]propyl]-1,1-dimethyl-2-[**naphthyl**]ethylamine; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol; and (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[(3-(2-aminophenoxy)-4-carboxy)phenoxy]-propan-2-ol; and a pharmaceutically acceptable salt or complex thereof.

6. A compound according to claim 5 selected from the group consisting of: (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(carbethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-

5-(carbethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[(3-(2-aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-(4-(2-phenyl-2-R,S-methoxycarbonyl)phenoxy)-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(3-benzyl-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[(3-benzyl-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[(3-benzyl-4-carboxymethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-cyano-4-ethoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[(2-nitro-4-methoxycarbonylmethyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[(4-methoxycarbonyl)phenoxy]-propan-2-ol; N-[2R-hydroxy-3-[[2-nitro-4-[2S-ethoxycarbonyl-2-[methylsulfonyl]amino]phenoxy]propyl]-1,1-dimethyl-2-[4-methoxyphenyl]ethylamine; N-[2R-hydroxy-3-[[2-nitro-4-[2S-methoxycarbonyl-2-[[2-carboxy]phenyl]carbonyl]amino]ethyl]phenoxy]propyl]-1,1-dimethyl-2-[naphthyl]ethylamine; and a pharmaceutically acceptable salt or complex thereof.

7. A compound according to claim 6 selected from the group consisting of: (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(2-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carbethoxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxypropyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(2-carbethoxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-3-(3-carboxyethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(carbethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(carboxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(carbethoxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-5-(carboxymethyl)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carbethoxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; (R)-N-[2-Hydroxy-3-(2-cyano-4-(2-carboxy-trans-ethylene)phenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; and (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[(3-(2-aminophenoxy)-4-methoxycarbonyl)phenoxy]-propan-2-ol; and a pharmaceutically acceptable salt or complex thereof.

. . . selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia, malignancy and **osteoporosis**.

12. A method according to claim 10 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 12 OF 26 USPATFULL on STN
AN 2002:99608 USPATFULL
TI **Calcilytic** compounds and method of use
IN Bhatnagar, Pradip Kumar, Exton, PA, UNITED STATES
Callahan, James Francis, Philadelphia, PA, UNITED STATES
Del Mar, Eric G., Salt Lake City, UT, UNITED STATES
Lago, Maria Amparo, Audubon, PA, UNITED STATES
PA SmithKline Beecham Corporation (U.S. corporation)
PI US 2002052509 A1 20020502
AI US 2001-5490 A1 20011204 (10)
RLI Continuation of Ser. No. US 2000-647794, filed on 5 Oct 2000, PENDING A
371 of International Ser. No. WO 1999-US7760, filed on 8 Apr 1999,
UNKNOWN
PRAI US 1998-81087P 19980408 (60)
DT Utility
FS APPLICATION
LREP GLAXOSMITHKLINE, Corporate Intellectual Property - UW2220, P.O. Box
1539, King of Prussia, PA, 19406-0939
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1533
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Calcilytic** compounds and compositions and their use in
treating abnormal bone or mineral homeostasis.
TI **Calcilytic** compounds and method of use
AB **Calcilytic** compounds and compositions and their use in
treating abnormal bone or mineral homeostasis.
SUMM [0001] The present invention relates to novel **calcilytic**
compounds, pharmaceutical compositions containing these compounds and
their use as calcium receptor antagonists.
SUMM [0006] Various compounds are known to mimic the effects of
extra-cellular Ca.sup.2+ on a calcium receptor molecule.
Calcilytics are compounds able to inhibit calcium receptor
activity, thereby causing a decrease in one or more calcium receptor
activities evoked by extracellular Ca.sup.2+. **Calcilytics** are
useful as lead molecules in the discovery, development, design,
modification and/or construction of useful calcium modulators which are
active at Ca.sup.2+ receptors. Such **calcilytics** are useful in
the treatment of various disease states characterized by abnormal levels
of one or more components, e.g., polypeptides. . . secretion of which
is regulated or affected by activity at one or more Ca.sup.2+ receptors.
Target diseases or disorders for **calcilytic** compounds include
diseases involving abnormal bone and mineral homeostasis.
SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture
healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral
hypercalcemia associated with malignancy and fracture healing, and
osteoporosis.
SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture
healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral
hypercalcemia associated with malignancy and fracture healing, and
osteoporosis.
SUMM [0018] R.sub.3 and R.sub.4 are, independently, methyl or ethyl
, or, together, form cyclopropyl;

SUMM . . . systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and **naphthyl**. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halo, C.sub.1-4 alkyl, OCF.sub.3, CF.sub.3, OMe, . . .

SUMM [0131] (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(2,3-dihydrobenzo[b]furan-5yl)**ethyl amine**;

SUMM . . . was used. This method can also be used for aryl alcohols. A solution of the substituted glycidyl ether and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine) in absolute ethanol, acetonitrile, TBF or any other similar solvent in the presence of a suitable catalyst such. . .

SUMM . . . and it is described in Scheme 2. The reduction of the oxime obtained from 3-quinolinecarboxaldehyde leads to the corresponding benzylic **amine**. Reaction of the aforementioned **amine** with 2,4,6-triphenylpyrylium tetrafluoroborate followed by nucleophilic displacement of the pyridinium salt thus formed with the anion of 2-nitropropane, leads to. . .

SUMM . . . amines, and it is described in Scheme 3. The Curtius rearrangement of 2,2-dimethyl-4-pentenoic acid leads to the corresponding Cbz protected **amine**. Addition of 9-BBN to the terminal olefin of the protected **amine** leads to the corresponding boronate. Palladium catalyzed coupling reaction between the boronate and the corresponding aryl bromide (2-bromopyridine in Scheme 3) leads to the formation of the corresponding **amine** after the removal of the protecting group.

SUMM . . . formed from isopropyltriphenylphosphonium leads to the corresponding olefin. Ritter reaction on the olefin followed by hydrolysis leads to the corresponding **amine**.

SUMM [0154] The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM [0158] The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50, . . .

SUMM . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.

SUMM [0178] **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

SUMM [0188] 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

SUMM [0192] A typical reaction mixture contains 2 nM .sup.3H compound ((R,R)-N4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-**naphthyl**)ethylamine), or .sup.3H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume. . .

DETD . . . ether and water. The ether layer was separated, dried over sodium sulfate and concentrated in vacuo to yield the crude **amine** as a dark oil. The product was purified by short-path distillation at reduced pressure.

DETD . . . mixture was poured into water, and washed with ether. The aqueous layer was then made basic with NaOH, and the **amine**

extracted into ether. The ether layer was separated, dried over sodium sulfate and concentrated in vacuo to yield 8.68 g of 3-(aminomethyl)quinoline. To this **amine** (8.68 g, 54.9 mmole), dissolved in 200 mL of dichloromethane, was added 2,4,6-triphenylpyrylium tetrafluoroborate (19.56 g, 49.4 mmole), and the.

- DETD Preparation of (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl-1,1-dimethyl-4-(2-carbethoxyphenyl)butylamine Hydrochloride **Ethyl** 2-(4-Amino-4-methylpentylbenzoate
- DETD [0219] To **ethyl** 2-bromobenzoate (0.504 g, 2.2 mmole) in a nitrogen flushed reaction tube was added 0.049 g (0.06 mmole) of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane. . . NaOH, and extracted with ether. The ether layer was dried over sodium sulfate, and concentrated in vacuo to give crude **ethyl** 2-(4-amino-4-methylpentyl)benzoate. The crude product was purified by reversed-phase HPLC on a C-18 column using a gradient of 0.1 % HCl. . .
- DETD [0224] 4 mmoles 5-**ethyl**-2-methyl pyridine in 4 mL dry ether was treated with 4.32 mmoles of phenyl lithium (1.8 M solution in cyclohexane/ether) at. . .
- DETD Preparation of 1,1-dimethyl-2-[(**ethyl**-4-oxyacetate)-phenyl]ethylamine
- CLM What is claimed is:
- . . . is selected from the group consisting of H, C.sub.1-4 alkyl, and C.sub.3-6 cycloalkyl; R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or, together, form cyclopropyl; R.sub.5 is heteroaryl or fused heteroaryl; wherein the hetero-ring contains N, O or S, and is. . .
- . . . selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia, malignancy and **osteoporosis**.

12. A method according to claim 11 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 13 OF 26 USPTAFULL on STN

AN 2002:63942 USPTAFULL

TI Calcium receptor active compounds

IN Sakai, Teruyuki, Gunma, JAPAN
Takami, Atsuya, Gunma, JAPAN
Nagao, Rika, Gunma, JAPAN

PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)

PI US 6362231 B1 20020326
WO 9801417 19980115

AI US 1999-214552 19990606 (9)
WO 1997-JP2358 19970708
19990617 PCT 371 date

PRAI JP 1996-178315 19960708
JP 1996-350393 19961227
JP 1997-107778 19970424

DT Utility

FS GRANTED

EXNAM Primary Examiner: Ramsuer, Robert W.

LREP Warburg, Richard J., Foley & Lardner

CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN 96 Drawing Figure(s); 94 Drawing Page(s)

LN.CNT 10207

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.P--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl)amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

- SUMM . . . one or more of the rings has a completely conjugated pi-electron system. Examples, without limitation, of aryl groups, are phenyl, **naphthyl**, anthracenyl, phenanthrenyl, fluorenyl, and indanyl. The aryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably. . .
- SUMM . . . or more halogens and, combined, unsubstituted cycloalkyl and cycloalkenyl. Also preferably, Ar.sub.1 is selected from the group consisting of phenyl, **naphthyl**, indolyl, fluorenyl, dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl, pyridin-4-yl, quinolin-2-yl and dibenzylamino and Ar.sub.2 is selected from the group consisting of phenyl, **naphthyl**, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl. More preferably, Ar.sub.1 is phenyl substituted with one. . . alkoxy, trihalomethoxy, trihaloacetyl and nitro, and Ar.sub.2 is selected from the group consisting of optionally substituted phenyl and optionally substituted **naphthyl**. Even more preferably, Ar.sub.2 is 3-methoxyphenyl or unsubstituted **naphthyl**. Preferably, R.sup.8 is hydrogen, R.sup.9 is methyl and X is oxygen or sulfur.
- SUMM . . . halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted **naphthyl**; and Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from. . . one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted **naphthyl**.
- SUMM . . . substituted with one or more halogens and lower alkoxy substituted with one or more halogens; and Ar.sub.6 is 3-methoxyphenyl or .alpha.-**naphthyl**, more preferably, .alpha.-**naphthyl**. Also preferably, Ar.sub.5 is dibenzylamino, benzyl(**naphthylmethyl**)amino or benzyl(**pyridylmethyl**)amino optionally substituted with one or more groups independently selected from the group. . . lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens, and Ar.sub.6 is **naphthyl** or methoxyphenyl. More preferably, Ar.sub.5 is dibenzylamino optionally substituted with unsubstituted alkyl, and Ar.sub.6 is .alpha.-**naphthyl**.
- SUMM . . . the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (calcimimetic modulation) or blocking the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (**calcilytic** modulation); preferably calcimimetic modulation.

SUMM . . . aspect, the present invention provides a method for the treatment or prevention of primary and secondary hyperparathyroidism, renalosteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering a therapeutically effective amount of a compound of this invention to a patient.

SUMM . . . affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, **osteoporosis** is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic . . . levels (e.g., a parathyroid cell ionmimetic) can retard bone loss and, thus, result in beneficial effects to patients suffering from **osteoporosis**.

SUMM . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from **osteoporosis**.

SUMM . . . modulates one or more effects of an inorganic ion receptor. Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and **calcilytics**.

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. **Calcilytics** are ionlytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium. . .

SUMM . . . preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis**, renalosteodystrophy and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as.

SUMM . . . Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism, renalosteodystrophy and **osteoporosis**.

DETD . . . mimic or block an effect of extracellular $\text{Ca}_{\text{sup.2+}}$ on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and **calcilytics**.

DETD Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC_{50} or IC_{50} at a calcium receptor of less than or equal to 5 mM, and even more. . .

DETD In another preferred embodiment the calcium receptor modulating agent is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . .

DETD . . . need not possess all the biological activities of extracellular $\text{Ca}_{\text{sup.2+}}$, but, rather, at least one such activity is mimicked. Similarly, **calcilytics** need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular $\text{Ca}_{\text{sup.2+}}$ to exert their. . .

DETD **B. Calcilytics**

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature

and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

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DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was added to the reaction mixture. Then the mixture was stirred at room temperature, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 17.31 g (87.8%) of colorless prism crystals 48.

DETD . . . 6 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 36.8 g (82.8%) of colorless prism crystals 49.

DETD . . . OC for 2.5 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl**

acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . OC for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 52.

DETD . . . (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 162.7 mg (0.95 mmol, 2.0 moleq.) of (R)-1-(1-**naphthyl**)ethylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an. . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 53.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 723.4 mg (87.0%) of a colorless oil 55.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 56.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 202.4 mg (73.3%) of a colorless prism crystals 58.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a

colorless oil 59.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 824.0 mg (84.9%) of a colorless oil 61.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 222.6 mg (87.1%) of a colorless oil 62.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 884.2 mg (91.1%) of a colorless oil 64.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 229.3 mg (89.7%) of a colorless oil 65.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 876.5 mg (90.3%) of a colorless oil 67.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 293.1 mg (87.2%) of a colorless oil 68.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 804.3 mg (77.0%) of colorless prism crystals 70.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the

obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 880.8 mg (89.5%) of a colorless oil 71.

DETD . . . temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 551.8 mg (100%) of a colorless oil 73.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 230.8 mg (91.3%) of a colorless oil 74.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 241.3 mg (45.9%) of a colorless oil 76.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 209.8 mg (69.7%) of a colorless oil 77.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 586 mg (61.4%) of a colorless oil 79.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 265.1 mg (82.8%) of a colorless oil 80.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 564.9 mg (82.5%) of colorless prism crystals 82.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a

saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 311.9 mg (83.8%) of colorless prism crystals 83.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 85.

DETD . . . acidified with a 5% aqueous solution of hydrochloric acid. Then the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 86.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 615.4 mg (98.5%) of colorless prism crystals 87.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with **ethyl** acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 76.3 mg (82.6%) of a colorless oil 88.

DETD To a solution of 600 mg (3.5 mmol) of (R)-1-(1-naphthyl)ethylamine 89 in 5 ml of methylene chloride were added 580.3 mg (d=1.176, 3.85 mmol, 1.1 moleq.) of ethylmalonyl chloride and . . . and dried over sodium sulfate. After distilling off the solvent, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 662.9 mg (66.5%) of colorless prism crystals 90.

DETD . . . concentrated, acidified with a 5% aqueous solution of hydrochloric acid. The reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 596.0 mg (99.8%) of colorless prism crystals 91.

DETD . . . (1.56 mmol) of the compound 91 in 5 ml of dimethylformamide were added 293.2 mg (1.71 mmol, 1.1 moleq.) of (R)-1-(1-naphthyl)ethylamine and 359.2 mg (1.87 mmol, 1.2 moleq.) of WSC.times.HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 615.1 mg (96.4%) of colorless prism crystals 92.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with **ethyl** acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 82.0 mg (88.0%) of a colorless oil 93.

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 361.8 mg (80.0%) of the compound 102 as colorless prisms.

DETD . . . a solution of the above compound 102 (125.8 mg, 0.38 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.1 mg (89.5%) of the compound 103 as a colorless oil.

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, n-hexane/**ethyl** acetate] to thereby give the compound 105 (723.4 mg, 87.0%) as a colorless oil.

DETD . . . a solution of the above compound 105 (106.2 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (48.4 mg, 0.35 mmol, 1.2 mol eq.) and the resulting mixture was stirred. . .

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 33.7 mg (76.1%) of the compound 106 as a colorless oil.

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 804.3 mg (77.0 %) of the compound 108 as colorless prisms.

DETD . . . a solution of the above compound 108 (106.9 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.2 mg (58.3%) of the compound 109 as a colorless oil.

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 586 mg (61.4%) of the compound 111 as a colorless oil.

DETD . . . a solution of the above compound 111 (65.3 mg, 0.26 mmol, 1.5 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (29.3 mg, 0.17 mmol) and potassium carbonate (35.5 mg, 0.26 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 36.5 mg (62.0%) of the compound 112 as a colorless oil.

DETD To a solution of (R)-(+)-1-(1-**naphthyl**)ethylamine (600 mg, 3.5 mmol) in dichloromethane (5 ml) were added ethylmalonyl chloride 113 (580.3 mg, 3.85 mmol, 1.1 mol eq.). . .

DETD . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 662.9 mg (66.5%) of the compound 114 as colorless prisms.

DETD . . . the reaction mixture was concentrated, acidified with a 5% aqueous solution of hydrochloric acid, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed successively with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 659.5 mg of the compound 115 as colorless prisms.

DETD To a solution of the above compound 115 (50 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (45.0 mg, 0.21 mmol, 1.1 mol eq.) and WSC.HCl (44.9 mg, 0.23 mmol, 1.2 mol eq.) and the resulting mixture. . .

DETD After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 61.6 mg (70.5%) of the compound 116 as colorless prisms.

DETD . . . into the reaction mixture. Then the mixture was acidified with a 5% aqueous solution of hydrochloric acid and extracted with **ethyl** acetate. The layer of the 5% aqueous solution of hydrochloric acid was made alkaline by adding a 5% aqueous solution of sodium hydroxide and then extracted with **ethyl** acetate. After washing with water and a saturated aqueous solution of sodium chloride

and drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 18.0 mg (88.0%) of the compound 117 as a colorless oil.

DETD After the completion of the reaction, ammonium chloride was added thereto in excess and the reaction mixture was extracted with **ethyl** acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 16.0 g of the compound 119.

DETD After cooling by allowing to stand, it was purified by column chromatography and eluted with **ethyl** acetate/n-hexane to thereby give 700 mg of the compound 120.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 1.5 g of the compound 122.

DETD The above compound 122 (150 mg, 0.51 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (104.5 mg, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (3 ml) and then allowed to stand at room. . .

DETD Synthesis of K-2027 (N-{5-[(4-chlorophenyl)thio]pentyl}N-[(1R)-1-(1-**naphthyl**)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (241 mg, 1.74 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.31 ml, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . C. for 24 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.70 g, 12.3 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.45 ml, 2.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2052 (N-{5-[(4-fluorophenyl)thio]pentyl}-N-[(1 R)-1-(1-**naphthyl**)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (300 mg, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (247 mg, 1.79 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2076 (N-[(1 R)-1-(1-**naphthyl**)ethyl]-N-(5-[(4-(trifluoromethyl)phenyl)thio]pentyl)amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (200 mg, 1.45 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.28 ml, 1.73 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2087 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-(4-[(3-(trifluoromethyl)phenyl)thio]butyl)amine)

DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2117 ((R)-N-[1-(1'-**naphthyl**)ethyl

] -2-(2',5'-dichlorophenylthio) ethylamine)

DETD . . . ice-cooling for 2 hours. after confirming the completion of the reaction by TLC, potassium carbonate (4.0 g, 28.9 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (3.70 ml, 22.9 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD The compound thus obtained (50 mg, 0.20 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (41.0 mg, 0.24 mmol, 1.2 mol eq.) were dissolved in chloroform-methanol (2 ml) and allowed to stand at room temperature. . .

DETD Synthesis of K-2246 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-{[4-(trifluoromethyl)phenyl]thio}butyl)amine)

DETD . . . reaction by TLC, 5 ml of acetonitrile, 693 mg (5.01 mmol) of potassium carbonate and 0.49 ml (2.96 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD . . . reaction by TLC, 8 ml of acetonitrile, 853 mg (6.17 mmol) of potassium carbonate and 0.60 ml (3.63 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD Synthesis of K-2243 (N1,N1-di(4-chlorobenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue, and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD 100 mg (0.31 mmol) of the above-mentioned compound 125 and 64.2 mg (0.38 mmol, 1.2 mol eq.) of (R)-(+)-1-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2257 (N1,N1-di[4-(trifluoromethoxy)benzyl]-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD 450 mg (1.07 mmol) of the above-mentioned compound 127 and 220.7 mg (1.29 mmol, 1.2 mol eq.) of (R)-(+)-1-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 reduced pressure and the oil thus. . .

DETD Synthesis of K-2259 (N1,N1-di[4-(trifluoromethyl)benzyl]-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD 800 mg (2.06 mmol) of the above-mentioned compound 129 and 424.0 mg (2.48 mmol, 1.2 mol eq.) of (R)-(+)-1-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2247 (N1-benzyl-N1-(4-chlorobenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 202 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 204 (105.8 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 reduced pressure. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 206 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD Synthesis of K-2250 (N1-benzyl-N1-(3,4-dichlorobenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)
DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. to the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 208 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 210 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were

dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 212 (100 mg, 0.35 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (71.8 mg, 0.42 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 214 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . hours. After the completion of the reaction, the solvent was distilled off under pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 216 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 218 (800 mg, 1.63 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (33.7 mg, 1.95 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 220 (1 g, 3.13 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (642.2 mg, 3.75 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2262 (N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . Then the obtained mixture was stirred at room temperature for 12 hours. After the completion of the reaction, were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 222 (500 mg, 1.56 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (321.1 mg, 1.88 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2264 (N1-(3,4-dichlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtain residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 224 (800 mg, 2.06 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (387.7 mg, 2.26 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2265 (N1,N1-di(3,4-dichlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 225 (712.2 mg, 74.3%).

DETD The conjugated ketone compound 226 (280 mg, 0.72 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (148 mg, 0.864 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2266 (N1-(4-chlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 228 (800 mg, 2.26 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (425.4 mg, 2.48 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2267 (N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduce pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD The conjugated ketone compound 230 (600 mg, 1.69 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (347.2 mg, 2.03 mmol, 1.2 mol eq.) were

dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2270 (N1,N1-di(4-methoxybenzyl)-3-([(1R)-1-(1-naphthyl) ethyl]amino)propanamide)

DETD . . . the reaction, the solvent was acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 232 (450 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (297 mg, 1.74 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2272 (N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 233 (777.3 mg, 78.2%).

DETD The conjugated ketone compound 234 (350 mg, 0.87 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (178 mg, 1.04 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2283 (N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 235 (1.092 g, 98.1%).

DETD The conjugated ketone compound 236 (400 mg, 1.08 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (222 mg, 1.30 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2289 (N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-([(1R)-1-(1-naphthyl) ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduce pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 237 (711.8 mg, 74.8%).

DETD The conjugated ketone compound 238 (414 mg, 1.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (270 mg, 1.57 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2290 (N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD The conjugated ketone compound 240 (874.7 mg, 2.50 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (513.9 mg, 3.00 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2291 (N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the

washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD The conjugated ketone compound 242 (500 mg, 1.49 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (307 mg, 1.79 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2294 (N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-[[(1R)-1-(1-**naphthyl**)**ethyl**]amino]propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD The conjugated ketone compound 244 (1.5587 g, 4.67 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (959.6 mg, 5.60 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2299 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-[[(1R)-1-(1-**naphthyl**)**ethyl**]amino]propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD The conjugated ketone compound 246 (1.4568 g, 4.36 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (896.8 mg, 5.24 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2300 (N1,N1-di(4-methylbenzyl)-3-[[(1R)-1-(1-**naphthyl**)**ethyl**]amino]propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 247 (819.4 mg, 88.2%).

DETD The conjugated ketone compound 248 (400 mg, 1.43 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (295 mg, 1.72 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2309 (N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-[[(1R)-1-(1-**naphthyl**)**ethyl**]amino]propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 249 (827.0 mg, 76.8%).

DETD The conjugated ketone compound 250 (692.4 mg, 1.98 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (407 mg, 2.37 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2310 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-[[(1R)-1-(1-**naphthyl**)**ethyl**]amino]propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 251 (979.1 mg, 80.4%).

DETD The conjugated ketone compound 252 (685.1 mg, 1.96 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (403 mg, 2.36 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel,

hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 253 (944.0 mg, 83.4%).

DETD The conjugated ketone compound 254 (612.8 mg, 1.68 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (345 mg, 2.01 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD The conjugated ketone compound 256 (260.2 mg, 0.88 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (180 mg, 1.05 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2280 (N-[5-[(4-methoxyphenyl)thio]pentyl-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (931 mg, 6.75 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.52 ml, 3.22 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2281 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[(2,4,5-trichlorophenyl)thio]butyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (545 mg, 3.94 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.41 ml, 3.94 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2282 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[5-[(2,4,5-trichlorophenyl)thio]pentyl]amine)

DETD . . . temperature for 2.5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.00 g, 7.25 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.69 ml, 4.27 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2287 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[(4-(trifluoromethoxy)phenyl)thio]butyl]amine)

DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (710 mg, 5.14 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.53 ml, 3.28 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2288 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[5-[(4-(trifluoromethoxy)phenyl)thio]pentyl]amine)

DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (770 mg, 5.57 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.58 ml, 3.59 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2293 (N-4-[(4-chlorophenyl)thio]butyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (775 mg, 5.61 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.62 ml, 3.84 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2240 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[3-[(4-(trifluoromethyl)phenyl)thio]propyl]amine)

DETD Synthesis of K-2263 (N-[4-[(4-fluorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2269 (N-[4-[(3-methoxyphenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2271 (N-[[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2279 (N-[5-(3-methoxyphenyl)thio]pentyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2284 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)pentyl)amine)

DETD Synthesis of K-2286 (N-(6-[(4-chlorophenyl)thio]hexyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2292 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(7-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)heptyl)amine)

DETD Synthesis of K-2296 (N-([5-(2,5-dichlorophenyl)thio]pentyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2297 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-([2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio)butyl)amine)

DETD Synthesis of K-2298 (N-(4-[(2,5-dichlorophenyl)thio]butyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2301 (N-[(1R)-1-((1-naphthyl)ethyl)-N-(6-([4-(trifluoromethoxy)phenyl]thio)hexyl)amine)

DETD Synthesis of K-2302 (N-(4-[(2,4-dimethylphenyl)thio]butyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2303 (N-(5-[(2,4-dimethylphenyl)thio]pentyl)-N-[(1R)-1-((1-naphthyl)ethyl)amine)

DETD Synthesis of K-2304 (N-(4-[(4-methylphenyl)thio]butyl)-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2305 (N-(5-[(4-methylphenyl)thio]pentyl)-N-[(1R)-1-((1-naphthyl)ethyl)amine)

DETD . . . crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine respectively by 3-trifluoromethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -methylbenzylamine. $m/z=355$.

DETD . . . synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the (R)-(+)-3-methoxy- α -benzylmethylamine by (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. $m/z=419$.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but

.alpha.-benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

[illegible]

DET D

benzylmethylamine respectively by 4-methoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptopbenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=398.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptopbenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-

naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine. 400 MHz-.sup.1H-NMR 8.18 (1H, d, J=8.1 Hz), 7.84-7.87 (1H, m), 8.80 (1H, d, J=1.9 Hz), 7.73 (1H, d, J=8.3 Hz),. . .

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-o-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=444, 446.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but

replacing the 2,5-dimethylthiophenol and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=447.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-t but replacing the 2,5-dimethylthiophenol and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=408.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=422.

DETD . . . the one employed for the synthesis of S-i but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-x-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=375.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl) ethyl amine.

- DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl) ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl) ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=391.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=355.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-

.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiopheol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=424.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=438.

DETD . . . potassium carbonate (4.04 g) was added thereto. After 1 hour, water was added and the resulting mixture was extracted with **ethyl** acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crystals thus obtained were washed with chloroform to thereby give N-(2-(2',5'-dichlorophenylthio)**ethyl**)phthalimide (F-8) (8.28 g). MS m/z: 351 (M.sup.+).

DETD N-(2-(2',5'-Dichlorophenylthio)**ethyl**)phthalimide (F-8) (7.06 g) was added to ethanol (120 ml). After further adding hydrazine monohydrate (6.9 ml), the obtained mixture was. . .

DETD . . . ice-cooling. Then the mixture was brought to room temperature and stirred for 15 hours. The reaction mixture was concentrated and **ethyl** acetate and water were added thereto. The insoluble matters were filtered off and the organic layer was washed with a. . . sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol=50:1) to thereby give (.+-.)-N-(1-(3-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-12) (146 mg). MS m/z: 355 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimehtoxyacetophenone to thereby give (.+-.)-N-(1-(3,4-dimethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 385 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-methylacetophenone to thereby give (+)-N-(1-(3-methylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-14). MS m/z: 339 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-methylacetophenone to thereby give (+)-N-(1-(4-methylphenyl **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 339 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4',5'-trimethoxyacetophenone to thereby give (.+-.)-N-(1-(3,4,5-trimethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-16). MS m/z: 415 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxyacetophenone to thereby give (.+-.)-N-(1-(4-hydroxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-17). MS m/z: 341 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethyl)acetophenone to thereby give (.+-.)-N-(1-(3-trifluoromethylphenyl)**ethyl**

)-2-(2',5'-dichlorophenylthio)ethylamine (F-18). MS m/z: 393 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxy-3'-methoxyacetophenone to thereby give (+-)-N-(1-(4-hydroxy-3-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-21). MS m/z: 371 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-bromoacetophenone to thereby give (+)-N-(1-(4-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-22). MS m/z: 405 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-bromoacetophenone to thereby give (+)-N-(1-(3-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-23). MS m/z: 405 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-bromoacetophenone to thereby give (+-)-N-(1-(2-bromophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-24). MS m/z: 405 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dihydroxyacetophenone to thereby give (+-)-N-(1-(3,4-dihydroxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-29). MS m/z: 357 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dichloroacetophenone to thereby give (+-)-N-(1-(2,5-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-30). MS m/z: 395 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoro-4'-methoxyacetophenone to thereby give (+)-N-(1-(3-fluoro-4-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 373 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethoxy)acetophenone to thereby give (+-)-N-(1-(3-trifluoromethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 409 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethylacetophenone to thereby give (+-)-N-(1-(3,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-48). MS m/z: 353 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-chloroacetophenone to thereby give (+-)-N-(1-(2-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-49). MS m/z: 359 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-chloroacetophenone to thereby give (+-)-N-(1-(3-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-50). MS m/z: 359 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-chloroacetophenone to thereby give (+-)-N-(1-(4-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-51). MS m/z: 359 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoroacetophenone to thereby give (+-)-N-(1-(3-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-52). MS m/z: 343 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-fluoroacetophenone to thereby give (+-)-N-(1-(4-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-53). MS m/z: 343 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dimethylacetophenone to thereby give (+-)-N-(1-(2,5-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-54). MS m/z: 353 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dimethylacetophenone to thereby give (+-)-N-(1-(2,4-dimethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-55). MS m/z: 353 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dichloroacetophenone to thereby give (+-)-N-(1-(2,4-dichlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-57). MS m/z: 395 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dichloroacetophenone to thereby give (+-)-N-(1-(3,4-dichlorophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-58). MS m/z: 395 (M.sup.+).

DETD 3'-Hydroxyacetophenone (200 mg) was dissolved in acetonitrile (4 ml). After adding ethyl iodide (0.2 ml) and potassium carbonate (347 mg), the mixture was stirred at 70.degree. C. for 9 hours. After 9 hours, water and ethyl acetate were added to the reaction mixture followed by separation. The organic layer was washed with a saturated aqueous solution. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:ethyl acetate=8:1) to thereby give 204 mg of 3'-ethoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-ethoxyacetophenone to thereby give (+-)-N-(1-(3-ethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-63). MS m/z: 369 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-propyl iodide to thereby give 3'-n-propoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-propoxyacetophenone to thereby give (+)-N-(1-(3-n-propoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-64). MS m/z: 383 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-butyl iodide to thereby give 3'-n-butoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-butoxyacetophenone to thereby give (+-)-N-(1-(3-n-butoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-65). MS m/z: 397 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by n-hexyl bromide to thereby give 3'-n-hexyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-hexyloxyacetophenone to thereby give (+-)-N-(1-(3-n-hexyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2255). MS m/z: 425 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by isopropyl iodide to thereby give 3'-isopropoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isopropoxyacetophenone to thereby give (+-)-N-(1-(3-isopropoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-67). MS m/z: 383 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by dodecane iodide to thereby give 3'-dodecylxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-dodecyloxyacetophenone to thereby give (+-)-N-(1-(3-n-dodecyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-68). MS m/z: 509 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by isobutyl iodide to

thereby give 3'-isobutoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isobutoxyacetophenone to thereby give (.-.)-N-(1-(3-isobutoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-69). MS m/z: 397 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 4-chlorobenzyl bromide to thereby give 3'-(4-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-chlorobenzoyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(4-chlorobenzoyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2258). MS m/z: 465 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2-chlorobenzyl bromide to thereby give 3'-(2-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chlorobenzoyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(2-chlorobenzoyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-71). MS m/z: 465 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by benzyl bromide to thereby give 3'-benzyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-benzyloxyacetophenone to thereby give (.-.)-N-(1-(3-benzyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-72). MS m/z: 431 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2,6-dichlorobenzyl bromide to thereby give 3'-(2,6-dichlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2,6-dichlorobenzoyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(2,6-dichlorobenzoyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-73). MS m/z: 501 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 1-bromo-6-chlorohexane to thereby give 3'-(6-chlorohexyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(6-chlorohexyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(6-chlorohexyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2260). MS m/z: 459 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 1-bromo-6-chlorohexane to thereby give 3'-(2-chloroethoxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chloroethoxy)acetophenone to thereby give (.-.)-N-(1-(3-(2-chloroethoxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-75). MS m/z: 403 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 2-methylbenzyl bromide to thereby give 3'-(2-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-methylbenzyl)acetophenone to thereby give (.-.)-N-(1-(3-(2-methylbenzyl)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-76). MS m/z: 445 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by 4-methylbenzyl bromide to thereby give 3'-(4-methylbenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-methylbenzoyloxy)acetophenone to thereby give (.-.)-N-(1-(3-(4-methylbenzoyloxy)phenyl)ethyl

)-2-(2',5'-dichlorophenylthio)ethylamine (K-2268). MS m/z: 445 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylfuran to thereby give (.-)-N-(1-(2-(5-methyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-78). MS m/z: 329 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylfuran to thereby give (.-)-N-(1-(2-furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-79). MS m/z: 315 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-1-methylpyrrole to thereby give (.-)-N-(1-(2-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-80). MS m/z: 328 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (+)-N-(1-(2-thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-81). MS m/z: 331 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2,5-dimethylfuran to thereby give (.-)-N-(1-(3-(2,5-dimethyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-82). MS m/z: 343 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylthiophene to thereby give (+)-N-(1-(3-thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-83). MS m/z: 331 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylthiophene to thereby give (.-)-N-(1-(2-(5-methyl)thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-84). MS m/z: 345 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-1-methylpyrrole to thereby give (.-)-N-(1-(3-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-85). MS m/z: 329 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 5-acetyl-2,4-dimethylthiazole to thereby give (.-)-N-(1-(5-(2,4-dimethyl)thiazolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-86). MS m/z: 360 (M.sup.+).

DETD The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by cyclohexylmethyl bromide to thereby give 3'-(cyclohexylmethoxybenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(cyclohexylmethoxybenzyloxy)-acetophenone to thereby give (.-)-N-(1-(3-(cyclohexylmethoxybenzyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-90). MS m/z: 437 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyridine to thereby give (.-)-N-(1-(2-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-91). MS m/z: 327 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylpyridine to thereby give (.-)-N-(1-(3-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-92). MS m/z: 326 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4-acetylpyridine to thereby give (.-)-N-(1-(4-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-93). MS m/z: 326 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyrazine to thereby give (.-)-N-(1-(2-pyrazyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-94). MS m/z: 327 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2-(methylaminesulfonyl)thiophene to thereby give (.+.-)-N-(1-(3-(2-methylaminosulfonyl)thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-95). MS m/z: 425 (M.sup.+).

DETD The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylindole to thereby give (.+.-)-N-(1-(3-indolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-96). MS m/z: 364 (M.sup.+).

DETD . . . was heated under reflux for 30 minutes. Then it was brought back to room temperature and separated into aqueous and **ethyl** acetate layers. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=3:1) to thereby give 510 mg of a bromo compound. This bromo compound (500 mg) was dissolved in acetonitrile (10 ml) and potassium carbonate (763 mg) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.18 ml) was added thereto. After further adding tetrabutylammonium iodide (41 mg), the mixture was heated under reflux. After 2. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=2:1) to thereby give 280 mg of a F-97. MS m/z: 544 (M+1.sup.+).

DETD The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-111. MS m/z: 587 (M+1.sup.+).

DETD The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-112. MS m/z: 601 (M+1.sup.+).

DETD The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-113. MS m/z: 544 (M.sup.+).

DETD The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-114. MS m/z: 628 (M.sup.+).

DETD The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-115. MS m/z: 572 (M.sup.+).

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=363.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=377.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=405.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.
m/z=419.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.
m/z=433.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.
m/z=447.

CLM What is claimed is:

. . . 0 to 14, inclusive; R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are independently hydrogen, or alkyl; and Ar.sub.2 is naphthyl optionally substituted by one or more medium alkyl moieties, or a pharmaceutically acceptable salt or hydrate of said compound.

7. The compound, salt or hydrate of claim 6 wherein Ar₂ is unsubstituted naphthyl.

15. N-((1R)-1-(1-naphthyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine, N-((1R)-1-(1-naphthyl)ethyl)-N-(5-((4-(trifluoromethoxy)phenyl)thio)pentyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(4-((4-(trifluoromethoxy)phenyl)thio)butyl)amine, N-(4-((2,4-dimethylphenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(5-((4-trifluoromethyl)phenyl)thio)pentyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(4-((2,4,5-trichlorophenyl)thio)butyl)amine, N-(5-((4-chlorophenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(5-((2,4-dimethylphenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(4-((4-trifluoromethyl)phenyl)thio)butyl)amine, N-(4-((4-methylphenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(4-((4-chlorophenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(6-((4-(trifluoromethoxy)phenyl)thio)hexyl)amine, N-(5-((4-methoxyphenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(5-((2,4,5-trichlorophenyl)thio)pentyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(4-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thio)butyl)amine, N-(5-((2,5-dichlorophenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(5-((4-fluorophenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(6-((4-chlorophenyl)thio)hexyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(4-((3-methoxyphenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(5-((4-methylphenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-(4-((2,5-dichlorophenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)ethyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(5-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thio)pentyl)amine, N-((1R)-1-(1-naphthyl)ethyl)-N-(7-((2,3,5,6-

tetrafluoro-4-(trifluoromethyl)phenyl)thio)heptyl)amine,
 N-((5-(3-methoxyphenyl)thio)pentyl)-N-((1R)-1-(1-naphthyl)
ethyl)amine, N-((1R)-1-(1-naphthyl)
ethyl)-N-(3-((4-(trifluoromethyl)phenyl)thio)propyl)
amine, N-((1R)-1-(1-naphthyl)**ethyl**
)-N-(4-(3-(trifluoromethyl)phenyl)thio)butyl)amine,
 N-(4-(4-fluorophenyl)thio)butyl)-N-((1R)-1-(1-naphthyl)
ethyl)amine, or a salt or hydrate thereof.

. . . 28. A method for treating or preventing a disorder selected from the group consisting of hyperparathyroidism, renal osteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering to a patient a therapeutically effective amount of said compound, said salt, or said. . .

L2 ANSWER 14 OF 26 USPATFULL on STN
 AN 2002:1232 USPATFULL
 TI **Calcilytic** compounds
 IN Bhatnagar, Pradip, Exton, PA, United States
 Lago, Maria Amparo, Audubon, PA, United States
 PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
 PI US 6335338 B1 20020101
 WO 2000009491 20000224
 AI US 2001-762405 20010207 (9)
 WO 1999-US18377 19990812
 20010207 PCT 371 date
 PRAI US 1998-96336P 19980812 (60)
 DT Utility
 FS GRANTED
 EXNAM Primary Examiner: Ramsuer, Robert W.
 LREP Simon, Soma G., King, William T., Kinzig, Charles M.
 CLMN Number of Claims: 6
 ECL Exemplary Claim: 1
 DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
 LN.CNT 620
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Novel **calcilytic** compounds are provided.
 TI **Calcilytic** compounds
 AB Novel **calcilytic** compounds are provided.
 SUMM The present invention relates to novel **calcilytic** compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.
 SUMM Various compounds are known to mimic the effects of extra-cellular Ca.sup.2+ on a calcium receptor molecule. **Calcilytics** are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.
 SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.
 SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral

hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM As used herein, "A" is phenyl or **naphthyl**, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6. . . .

DETD . . . and the reaction was heated to reflux for 30 min. The solvent was evaporated and the residue was dissolved in **ethyl** acetate, washed with brine. The combined organic layers were dried (MgSO.sub.4) and the solvent was evaporated to yield a colorless. . . .

DETD . . . reaction mixture was heated to reflux overnight. After cooling the solvent was eliminated in vacuo, the residue was diluted with **ethyl** acetate and water. The organic layer was washed with diluted acid, and brine. The organic layer was dried MgSO.sub.4 and the solvent was evaporated to yield liquid that was purified by flash column chromatography (silica gel, 30% **ethyl** acetate/hexane) to obtain 260 mg of the desired compound as a colorless liquid followed by 600 mg of recovered starting. . . .

DETD 230 mg (0.65 mmol) of the Boc protected **amine** from 1b was treated with 5 mL of 4M .sup.HCl solution in dioxane for 30 min. The solvent was eliminated. . . .

DETD The free **amine** from Example 1b (145 mg, 0.57 mmol), 4-phenyl-chlorobutane (96 mg, 0.57 mmol) and NaI (0.33 mg, 0.57 mmol) were dissolved. . . . reaction mixture was heated to reflux overnight. After cooling to RT, the solvent was eliminated the residue was dissolved in **Ethyl** Acetate, washed with water. The organic layer was dried MgSO.sub.4 and the solvent was evaporated to yield a yellow liquid. . . .

DETD . . . 4.3 mmol). The mixture stirred 2 h at RT. The reaction mixture was concentrated to dryness in vacuo, diluted with **ethyl** acetate washed with water. The organic layer was dried (MgSO.sub.4) and the solvent was evaporated to yield a colorless liquid. . . .

DETD The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . . .

DETD The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . . .

DETD . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.

DETD **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . . .

DETD To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . . .

DETD A typical reaction mixture contains 2 nM .sup.3H compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-**naphthyl**)ethylamine), or .sup.3H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume. . . .

CLM What is claimed is:

. . . selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's

disease, humoral hypercalcemia, malignancy and **osteoporosis**.

5. A method according to claim 4 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 15 OF 26 USPATFULL on STN
AN 2001:197043 USPATFULL
TI Calcium receptor-active molecules
IN Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
DelMar, Eric G., Salt Lake City, UT, United States
Nemeth, Edward F., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 6313146 B1 20011106
AI US 1995-484159 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
Continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994
Continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned
Continuation-in-part of Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned
Continuation-in-part of Ser. No. US 1993-9384, filed on 23 Feb 1993, now abandoned
Continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned
Continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992
Continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned
Continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jones, Dwayne C.
CLMN Number of Claims: 55
ECL Exemplary Claim: 1
DRWN 174 Drawing Figure(s); 135 Drawing Page(s)
LN.CNT 6744
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.
SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an . . .
SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.
SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl,

indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;

SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinoliny, 2- or 3-indolyl, benzyl, and phenoxy.

SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.

SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.

SUMM More preferred compounds are those where R is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . . .

SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.

SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . . .

SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's". . . .

SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .

SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . . .

SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a cell. . . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium receptor, but not. . . .

SUMM . . . a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . . .

SUMM . . . a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM . . . 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM . . . receptor are useful to elucidate-which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM . . . calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular Ca.sup.2+ on $[\text{Ca.sup.2+}]_{\text{sub.i}}$ in bovine parathyroid cells. Cells were initially bathed in. . .

DETD . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca.sup.2+ receptors.

DETD . . . agents are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of Ca.sup.2+ at calcium receptors can be determined using procedures. . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular Ca.sup.2+ . In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP. . .

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular Ca.sup.2+ in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the EC.sub.50 or IC.sub.50 , the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca.sup.2+ , the importance of different functional groups for calcimimetics and **calcilytics** were identified of the molecules tested, some are suitable as drug-candidates while others are not necessarily suitable as drug candidates.. . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and

ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD . . . preferably linear, or more preferably branched hydrocarbon (sp² or preferably sp³ hybridization). Ar.sup.1 =(preferably) phenyl or 2naphthyl; Ar.sup.2 (preferably)=phenyl or 1-**naphthyl** R.sup.1 =(preferably) methyl, R.sup.2 =(preferably) H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1 -**naphthyl**, 2naphthyl, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydronaphthalenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . . .

DETD . . . A. Nelson and Thomas E. D'Ambra in U.S. patent application Ser. No. 276,214, issued as U.S. Pat. No. 5,504,253 entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-tert-butyl-dicarbonate (BOC. . . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially

protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10##

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium-receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or. . . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may

also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic Activity of NPS 021 on Parathyroid Cells**

DETD For a compound to be considered a **calcilytic**, it must block the effects of extracellular $\text{Ca}_{\text{sup.2+}}$ or a calcimimetic compound on an extracellular $\text{Ca}_{\text{sup.2+}}$ -sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}_{\text{sup.2+}}]_{\text{sub.i}}$ when tested at low $[\text{Ca}_{\text{sup.2+}}]$ (0.5 mM; FIG. 37). $\text{Ga}_{\text{sup.3+}}$ is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: $\text{Ga}_{\text{sup.3+}}$ by itself has no effect on the $\text{Cl}_{\text{sup.-}}$ currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic components of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular $\text{Ca}_{\text{sup.2+}}$. . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M

were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride. It was found for the syntheses of these three compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H) -mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**)ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . . .

DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**) **ethyl amine** hydrochloride

DETD A mixture of (R)-(+)-1-1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . . .

DETD (R)-N-3-(2-Methylphenyl)-1-propyl-3-methoxy-.alpha.-methylbenzyl **amine** hydrochloride

DETD (R)-N-3-(3-Methylphenyl)-1-propyl-3-methoxy-.alpha.-methylbenzyl **amine** hydrochloride

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamionitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.). . . chromatographed [Selectosil, 5-.mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . . .

DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)**ethyl**)7-(1-**naphthyl**)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . . .

DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1-(1-**naphthylethyl**)**amine**

DETD A mixture of 3'-chloro-4' -methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

AN 2001:163199 USPATFULL
 TI **Calcilytic** compounds
 IN Barmore, Robert M., Salt Lake City, UT, United States
 Bhatnagar, Pradip Kumar, Exton, PA, United States
 Bryan, William M., Phoenixville, PA, United States
 Burgess, Joelle Lorraine, Phoenixville, PA, United States
 Callahan, James Francis, Philadelphia, PA, United States
 Calvo, Raul Rolando, Royersford, PA, United States
 Del Mar, Eric G., Salt Lake City, UT, United States
 Lago, Maria Amparo, Audubon, PA, United States
 Nguyen, Thomas The, King of Prussia, PA, United States
 Sheehan, Derek, Salt Lake City, UT, United States
 Smith, Robert Lawrence, Lansdale, PA, United States
 Southall, Linda Sue, West Chester, PA, United States
 Van Wageningen, Bradford C., Salt Lake City, UT, United States
 PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
 PI US 6294531 B1 20010925
 WO 9845255 19981015
 AI US 1999-402310 19991001 (9)
 WO 1998-US6928 19980408
 19991001 PCT 371 date
 19991001 PCT 102(e) date
 PRAI US 1997-42724P 19970408 (60)
 US 1997-61327P 19971008 (60)
 US 1997-61329P 19971008 (60)
 US 1997-61330P 19971008 (60)
 US 1997-61333P 19971008 (60)
 US 1997-61331P 19971008 (60)
 DT Utility
 FS GRANTED
 EXNAM Primary Examiner: Powers, Fiona T.
 LREP Simon, Soma G., King, William T., Kinzig, Charles M.
 CLMN Number of Claims: 8
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 3114
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Novel arylalkylamino compounds exhibiting **calcilytic** properties are provided.
 TI **Calcilytic** compounds
 AB Novel arylalkylamino compounds exhibiting **calcilytic** properties are provided.
 SUMM The present invention relates to novel arylalkylamine **calcilytic** compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.
 SUMM Various compounds are known to mimic the effect of extra-cellular Ca.sup.2+ on a calcium receptor. **Calcilytics** are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e g., . . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.
 SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and

osteoporosis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis.**

SUMM . . . R¹ is C.sub.1-4 alkyl and n is an integer from 1 to 3, R.sub.3 and R.sub.4 are, independently, methyl or **ethyl**, or, together, form cyclopropyl;

SUMM R.sub.5 is phenyl or **naphthyl**, unsubstituted or substituted with one or more substituents selected from the group consisting of OH, C.sub.1-4 alkyl, halo, CH(CH.sub.3).sub.2, halo. . .

SUMM . . . systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and **naphthyl**. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halo, C.sub.1-4 alkyl, OCF.sub.3, CF.sub.3 OMe, . . .

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-ethylcarbonyl]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2,3-dichloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2,3-dichloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano, 3-chloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano, 3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-piperazinylcarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1,1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol;

SUMM N-[3-(3-chloro-2-cyano-4-pyrrolidinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-(4'-N-t-butoxycarbonylpiperazino)sulfamyl)phenoxy]-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10-ethylthio-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10-ethylthio-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10-ethylthio-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[3-oxy-10-oxo-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; and

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano,3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; and

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol. N-[3-(3-chloro-2-cyano-4-dimethylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-pyrrolidinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine;

SUMM N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[10-ethylthio-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; and

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol.

SUMM N-[3-(3-chloro-2-cyano-4-pyrrolidinylsulfonyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-morpholinylsulfonyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM N-[3-(3-chloro-2-cyano-4-thiomorpholinylsulfonyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol;

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10-ethylthio-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol; and

SUMM (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10-ethylthio-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene]-propan-2-ol;

SUMM . . . was used. This method can also be used for aryl alcohols. A solution of the substituted glycidyl ether and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine) in absolute ethanol, acetonitrile, THF or any other similar solvent in the presence of a suitable catalyst such. . .

SUMM . . . an appropriate sulfonyl or carbonyl chloride such as tosyl, or mesyl chloride or 4-morpholinecarbonyl chloride, in the presence or triethyl **amine** produces the corresponding sulfonamide or urea. Alkylation of the sulfonamide nitrogen can be carried out via deprotonation with an appropriate. . . the corresponding aryl alcohol. Treatment of an ortho-substituted aryl ether Scheme 4 with SOCl₂.sub.2 followed by a primary. or secondary **amine** gives the p-sulfonamide. The methyl ether is then removed with Me.sub.3 PhSi and I.sub.2 or with LiI in an appropriate. . .

SUMM The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .

SUMM . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**. Increasing serum PTH levels can be used to treat various diseases including bone and mineral related diseases.

SUMM **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

SUMM To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

SUMM A typical reaction mixture contains 2 nM .sup.3 H compound ((R,R)-N-4'-methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-**naphthyl**)ethylamine), 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume of 0.5 mL. Incubation. . .

SUMM In one embodiment of the present invention the **calcilytic** compounds have a K.sub.i.gtoreq.0.1 uM, at the .beta.-adrenergic

receptor as measured using the .beta.-Adrenergic Receptor Binding Assay described above. In other embodiments, using the .beta.-Adrenergic Receptor Assay **calcilytic** compounds have a $K_{sub.i}$ of $1.0 \mu\text{M}$ and $K_{sub.i}$ of $10.0 \mu\text{M}$.

DETD A mixture of Experiment 4e (0.36 g, 1 mmol), LiClO_4 (0.14 g, 1 mmol), and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.2 g, 1 mmol) in dried acetonitrile (8 mL) was heated at reflux in 24 h. The mixture was cooled. . . .

DETD . . . stirred at room temperature an additional 18 h. H_2O (150 mL) was added to quench the reaction then the **amine** was extracted into diethyl ether (3.times.100 mL). The organic layers were combined, washed with saturated NaCl(aq) (100 mL), dried over. . . .

DETD Following the procedure outlined in Example 10 but substituting propyl **amine** for dipropylamine in Example 10(a) 7 mg of the title compound was prepared. ESMS $[\text{M}+\text{H}]^+$ = 440; $^1\text{H NMR}$ (CDCl_3 , . . .

DETD Preparation of (R)-3-[2-cyano-4-[N-methyl-N'-morpholinolureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol;

DETD e) Synthesis of (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol.

DETD c) N-[2(R)-hydroxy-3-(3-chloro-2-cyanophenoxy-4-dimethylsulfonamidyl)propyl]-N-[2-(4-methoxyphenyl)-1,1-dimethylethyl] **amine** hydrochloride

DETD N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine hydrochloride

DETD N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine hydrochloride

DETD N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine hydrochloride

DETD Following the procedure of Example 15, substituting 1,1-dimethyl-2-(2-**naphthyl**)ethylamine for 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine in 15(e), the title compound was prepared (157 mg). MS (ES) m/e 581.2 $[\text{M}+\text{H}]^+$; $^1\text{H NMR}$

DETD N-[3-[3-chloro-2-cyano-4-(4'-N-t-butoxycarbonylpiperazino)sulfamoyl]phenoxy]-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine hydrochloride;

DETD e) Synthesis of (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol.

DETD d) Synthesis of (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-propan-2-ol.

DETD a) **Ethyl** 10,11-dihydro-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate.

DETD b) **Ethyl** 10,11-dihydro-3-hydroxyl-2-formyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate.

DETD A solution of **ethyl** 10,11-dihydro-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (2.9 g, 9.8 mmol), SnCl_4 (0.15 mL, 1.3 mmol) and tributylamine (1.2 mL, 5.2 mmol) in toluene (60 mL). . . . solution was cooled to RT and poured into water and acidified with aqueous HCl (3M) to pH 2 (litmus paper). **Ethyl** ether was added and the layers separated. The organic layer was washed with water and concentrated. Flash chromatography (silica gel, . . .

DETD c) **Ethyl** 10,11-dihydro-3-hydroxyl-2-imino-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate.

DETD A solution of **ethyl** 10,11-dihydro-3-hydroxyl-2-formyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (1.2 g, 3.8 mmol), hydroxylamine hydrochloride (0.68 g, 9.8 mmol) and triethylamine (1.4 mL, 10 mmol) in EtOH (20. . . .

DETD d) **Ethyl** 10,11-dihydro-2-cyano-3-oxyacetyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate.

DETD A solution of **ethyl** 10,11-dihydro-3-hydroxyl-2-imino-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (2.5 g, 3.8 mmol) in acetic anhydride (30 mL) was heated at reflux for 30 min. The solution was. . . .

DETD e) **Ethyl** 10,11-dihydro-2-cyano-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate.

DETD A solution of **ethyl** 10,11-dihydro-2-cyano-3-oxyacetyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (0.8 g, 2.2 mmol) in EtOH/water (1:1, 10 mL) was treated with K.sub.2 CO.sub.3 (0.76 g, 5.5 mmol). After. . .

DETD f) (2R)-Glycidyl-[**ethyl** 10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d] cycloheptene-10-(R)-acetate].

DETD A solution of **ethyl** 10,11-dihydro-2-cyano-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (0.67 g, 2.1 mmol), (2R)-glycidyl 3-nitrobenzenesulfonate (Aldrich Chemicals, 0.54 g, 2.1 mmol) and K.sub.2 CO.sub.3 (0.864 g, 6.3 mmol). . .

DETD g) (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl** -10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol hydrochloride salt

DETD A solution of (2R)-glycidyl-(**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate) (0.8 g, 2.1 mmol), 1,1-dimethyl-2-(4-methoxyphenyl)**ethyl** amine (0.375 g, 2.1 mmol) and LiClO.sub.4 (0.445 g, 4.2 mmol) in CH.sub.3 CN (10 mL) was heated at reflux for. . .

DETD A solution of (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol (0.6 g, 1.1 mmol) in EtOH/water (1:1, 4 mL) was treated with aqueous NaOH (1M, 2 mL, 2 mmol). After. . .

DETD Preparation of (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R/S)-acetate]-propan-2-ol

DETD a) (2R)-Glycidyl-(**ethyl**-10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R/S)-acetate)

DETD Following the procedure of Example 41 (f) except substituting **ethyl**-(R/S)-10,11-dihydro-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-acetate for compound of Example 41(e), 0.7 g of the title compound was prepared and used without further purification in the. . .

DETD b) (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl** -10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R/S)-acetate]-propan-2-ol hydrochloride salt

DETD Following the procedure of Example 41(g) except substituting (2R)-glycidyl-(**ethyl**-10,11-dihydro-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R/S)-acetate) (0.7 g, 2.1 mmol) for compound of Example 41(f), 0.44 g (45%) of the title compound was prepared. MS (ES) m/e. . .

DETD Following the procedure of Example 41 (h) except substituting (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl** -10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R/S)-acetate]-propan-2-ol hydrochloride salt for compound of Example 41 (g), 0.118 g (55%) of the title compound was prepared. MS (ES) m/e. . .

DETD Preparation of (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol hydrochloride salt.

DETD a) (2R)-Glycidyl **ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate

DETD Following the procedure of Example 41 (f) except substituting **ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (0.337 g, 1.1 mmol) for the compound of Example 41 (e), 0.37 g of the title compound was prepared and used. . .

DETD b) (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl** -10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol hydrochloride salt.

DETD Following the procedure of Example 41 (g) except substituting (2R)-glycidyl **ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate (0.37 g, 1.1 mmol) for the

compound of Example 41 (f), 0.125 g (22%) of the title compound was prepared.. . .

- DETD Following the procedure of Example 41 (h) except substituting (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10(R)-acetate]-propan-2-ol hydrochloride salt (0.07 g, 0.13 mmol) for the compound of Example 1 (g) 0.03 g (50%) of the title compound. . .
- DETD Preparation of (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10(S)-acetate]-propan-2-ol hydrochloride salt.
- DETD a) (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate]-propan-2-ol hydrochloride salt.
- DETD . . . 0.1% diethylamine). The pure diastereoisomers were converted to the corresponding HCl salts by treatment with HCl in MeOH to yield (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate]-propan-2-ol hydrochloride salt (20 mg) and (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol hydrochloride salt (20 mg) which was identical to material synthesized in Example 44 (b).
- DETD Preparation of (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate]-propan-2-ol hydrochloride salt.
- DETD a) **Ethyl**-10,11-dihydro-2-formyl-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate.
- DETD Following the procedure of Example 41 (b) except substituting **ethyl**-10,11-dihydro-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate (1.0 g, 3.4 mmol) for the compound of Example 41 (a) 0.9 g (41%) of the title compound was prepared.. . .
- DETD b) **Ethyl**-10,11-dihydro-2-iminohydroxyl-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate.
- DETD Following the procedure of Example 41 (c) except substituting **ethyl**-10,11-dihydro-2-formyl-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate (0.9 g, 2.8 mmol) for the compound of Example 41 (b) 0.9 g of the title compound was prepared and used. . .
- DETD c) **Ethyl**-10,11-dihydro-2-cyano-3-hydroxyacetyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate:
- DETD Following the procedure of Example 41 (d) except substituting **ethyl**-10,11-dihydro-2-iminohydroxyl-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate (0.9 g, 2.6 mmol) for the compound of Example 41 (c) 0.3 g (32%) of the title compound was prepared. .sup.l. . .
- DETD d) **Ethyl**-10,11-dihydro-2-cyano-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate.
- DETD Following the procedure of Example 41 (e) except substituting **ethyl**-10,11-dihydro-2-cyano-3-hydroxyacetyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate (0.3 g, 2.6 mmol) for the compound of Example 41 (d) 0.3 g (75%) of the title compound was prepared.. . .
- DETD e) (2R)-Glycidyl-(**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate).
- DETD Following the procedure of Example 41 (f) except substituting **ethyl**-10,11-dihydro-2-cyano-3-hydroxyl-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate (0.2 g, 0.6 mmol) for the compound of Example 41 (e) 0.2 g (87%) of the title compound was prepared and used. . .
- DETD f) (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate]-propan-2-ol hydrochloride salt.

DETD Following the procedure of Example 41 (g) except substituting (2R)-glycidyl-(**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate). (0.23 g, 0.62 mmol) for the compound of Example 41 (f) 0.3 g (86%) of the title compound was prepared. MS. . . .

DETD Preparation of (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol hydrochloride salt.

DETD a) (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetic acid]-propan-2-ol hydrochloride salt.

DETD Following the procedure of Example 41 (h) except substituting (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(S)-acetate]-propan-2-ol hydrochloride salt (0.14 g, 0.24 mmol) for the compound of Example 41 (g) 0.066 g (50%) of the title compound. . . .

DETD Preparation of (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[3-oxy-10-ethylthio-5H-dibenzo[a,d]cycloheptene]-propan-2-ol hydrochloride salt.

DETD a) (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[3-oxy-10-ethylthio-5H-dibenzo[a,d]cycloheptene]-propan-2-ol hydrochloride salt.

DETD Preparation of (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10(R)-acetate]-propan-2-ol hydrochloride salt.

DETD a) (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate]-propan-2-ol hydrochloride salt.

DETD A solution of (2R)-glycidyl-(**ethyl**-10,11-dihydro-2-cyano-3-oxy-5H-dibenzo[a,d]cycloheptene-10-(R)-acetate) (0.8 g, 2.1 mmol), 1,1-dimethyl-2-(4-methoxyphenyl)**ethyl amine** (0.375 g, 2.1 mmol) and LiClO₄ (0.445 g, 4.2 mmol) in CH₂Cl₂ (10 mL) was heated at reflux for. . . .

DETD . . . mL) was heated to 110.degree. C. for 18 h. The solution was diluted with water (200 mL) and extracted with **ethyl** acetate. The **ethyl** acetate layer was concentrated to give the crude title compound which was used as is for the next step (57. . . .

DETD . . . and allowed to run at RT for 18 h. The reaction solution was poured into a 5% NaHCO₃ solution and **ethyl** acetate was added. The **ethyl** acetate layer was separated and washed with water (2.times.) and brine (1.times.). The **ethyl** acetate layer was concentrated to give the title compound (7.4 g, 91%): .sup.1 H NMR (400 MHz, DMSO-d₆) .delta. 3.8-3.9. . . .

DETD A solution of 2R-glycidyl-(9-oxy-dibenz[b,f][1,4]oxazepin-11(10H) (0.10 g, 0.4 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)**ethyl amine** (0.07 g, 0.4 mmol) in EtOH (5 mL) was heated to reflux for 18 hr. The solution was concentrated. and. . . .

DETD a) **Ethyl**-3-methoxy-dibenz[b,f][1,4]azepine-11(10H)-acetate

DETD b) **Ethyl**-3-hydroxy-dibenz[b,f][1,4]azepine-11(10H)-acetate

DETD Following the procedure of Example 53 (d) except substituting **ethyl**-3-methoxy-dibenz[b,f][1,4]azepine-11(10H)-acetate (1.2 g, 4.4 mmol) for the compound of Example 53 (c) the crude title compound was prepared and used as. . . .

DETD c) **Ethyl** 2R-Glycidyl-(3-oxy-dibenz[b,f][1,4]azepin-11(10H)acetate

DETD Following the procedure of Example 53 (e) except substituting **ethyl**-3-hydroxy-dibenz[b,f][1,4]azepine-11(10H)-acetate (1.6 g, 4.4 mmol) for the compound of Example 53 (d) the crude title compound was prepared and used as. . . .

DETD Following the procedure of Example 53 (f) except substituting **ethyl** 2R-glycidyl-(3-oxy-dibenz[b,f][1,4]azepin-11(10H)acetate (0.09 g, 0.25 mmol) for the compound of Example 53 (g) the title compound was prepared (0.07 g,

CLM

What is claimed is:

1. A compound selected from the group consisting of:
(R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-methyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-methyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-methylsulfonylamino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(benzyloxy)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-3-phenylpropylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-4-phenylbutylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-ethylcarbonyl]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol;
(R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-propylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol;
(R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2,3-dichloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2,3-dichloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2,3-dichloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2,3-dichloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-piperazinylcarbonyl)phenoxy]-propan-2-ol;
(R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-

(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-morpholinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-piperazinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-**naphthyl**)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-3-(phenyl)propylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-4-(phenyl)butylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-3-(phenoxy)propylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(oxybenzyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; N-[3-(3-chloro-2-cyano-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2,3-dichlorophenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-dimethylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)-cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)-cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(benzyl-cyclopropyl)sulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(benzyl-cyclopropyl)sulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(4'-N-t-butoxycarbonylpiperazino)sulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(4'-N-t-butoxycarbonylpiperazino)sulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-**naphthyl**)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-pyrrolidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-pyridinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-cyclopropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-propylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-sulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-methylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-fluorophenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(benzyloxy)-1,1-dimethylethylamine;

N-[3-(2,3-dichloro-4-morpholinofamyl)phenoxy-2(R)-hydroxypropyl]-3-phenyl-1,1-dimethylpropylamine; N-[3-(2,3-dichloro-4-morpholinofamyl)phenoxy-2(R)-hydroxypropyl]-4-phenyl-1,1-dimethylbutylamine; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 selected from the group consisting of: (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-(2-cyano-4-[N-methyl-N-[4-methylphenylsulfonyl]amino]phenoxy)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methylsulfonylamino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano, 3-chloro-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; N-[3-(3-chloro-2-cyano-4-dimethylsulfonyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-morpholinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinofamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-(benzylcyclopropyl)sulfonyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-

dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(benzyl-cyclopropyl)sulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-pyrrolidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-piperidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethyl-ethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)-cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)-cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(benzyloxy)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-dipropylsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(benzyloxy)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-3-phenyl-1,1-dimethylpropylamine; N-[3-(2,3-dichloro-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-4-phenyl-1,1-dimethylbutylamine; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 selected from the group consisting of: (R)-3-[2-cyano-4-[N-benzyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N-[4-methylphenylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N-[methylsulfonyl]amino]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-benzyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-3-[2-cyano-4-[N-methyl-N'-morpholino]ureido]phenoxy]-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N,N-dipropylaminocarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-piperidinylcarbonyl)phenoxy]-propan-2-ol; (R)-1-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-3-[2-cyano-4-(N-pyrrolidinylcarbonyl)phenoxy]-propan-2-ol; N-[3-(2,3-dichloro-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-pyrrolidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl

-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-thiomorpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-pyrrolidinolsulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-piperidinolsulfamoyl)phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(benzyloxy)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(4-methoxyphenyl)-1,1-dimethylethylamine; N-[3-[3-chloro-2-cyano-4-(2'-cyanoeth-1-yl)-cyclopropylsulfamoyl]phenoxy-2(R)-hydroxypropyl]-2-(2-naphthyl)-1,1-dimethylethylamine; N-[3-(3-chloro-2-cyano-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-2-(benzyloxy)-1,1-dimethylethylamine; N-[3-(2,3-dichloro-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-4-phenyl-1,1-dimethylbutylamine; N-[3-(2,3-dichloro-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-3-phenyl-1,1-dimethylpropylamine; N-[3-(2,3-dichloro-4-morpholinosulfamyl)phenoxy-2(R)-hydroxypropyl]-4-phenyl-1,1-dimethylbutylamine; or a pharmaceutically salt thereof.

. . . selected from the group consisting of: osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

7. A method according to claim 6 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 17 OF 26 USPATFULL on STN
AN 2001:158282 USPATFULL
TI **Calcilytic** compounds
IN Bhatnagar, Pradip, Exton, PA, United States
Lago, Maria Amparo, Audubon, PA, United States
PA SmithKline Beecham Corporation, United States (U.S. corporation)
PI US 6291459 B1 20010918
WO 2000009132 20000224
AI US 2001-762413 20010409 (9)
WO 1999-US18378 19990812
20010409 PCT 371 date
20010409 PCT 102(e) date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Higel, Floyd D.; Assistant Examiner: Shameem, Golam M.
M.
LREP Simon, Soma G., King, William T., Kinzig, Charles M.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 679
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound selected from Formula (I) hereinbelow: ##STR1##

or a pharmaceutically acceptable salt thereof, wherein

m is an integer from 0 to 2; n is an integer from 1 to 3;

X is selected from the group consisting of CN, NO.sub.2, Cl, F, and H;

Y is selected from the group consisting of Cl, F, Br, I and H; and

Q and Z are, independently, selected from the group consisting of H, R.sub.1, SO.sub.2 R.sub.1 ', R.sub.1 C(O)OR.sub.1 ", SO.sub.2 NR.sub.1 'R.sub.1 ", C(O)NR.sub.1 'R.sub.1 ", NR.sub.1 'SO.sub.2 R".sub.1, wherein R1, R.sub.1 ' and R.sub.1 " are independently selected from the group consisting of hydrogen, C.sub.1-4 alkyl, C.sub.3-6 cycloalkyl, C.sub.2-5 alkenyl, C.sub.2-5 alkynyl, heterocycloalkyl, aryl and aryl C.sub.1-4 alkyl; or R.sub.1 ' and R.sub.1 " together form a 3 to 7 membered optionally substituted heterocyclic ring; wherein any substituents are selected from the group consisting of CN, aryl, CO.sub.2 R, CO.sub.2 NHR, OH, OR, NH.sub.2, halo, CF.sub.3, OCF.sub.3 and NO.sub.2 ; wherein R represents H, C.sub.1-4 alkyl, and C.sub.3-6 cycloalkyl; and A is phenyl or **naphthyl**, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6 cycloalkyl, OSO.sub.2 R.sub.1, CN, NO.sub.2, OCF.sub.3, CF.sub.3, and CH.sub.2 CF.sub.3, (CH.sub.2).sub.n CO.sub.2 H, (CH.sub.2).sub.n CO.sub.2 R.sub.1, and O--(CH.sub.2).sub.n CO.sub.2 R.sub.1, wherein n is an integer from 0 to 3 0-3 and R.sub.1 represents C.sub.1-4 alkyl, C.sub.3-6 cycloalkyl, C.sub.3-6 cycloalkyl, heteroaryl or fused heteroaryl (wherein the hetero-ring can contain N, O or S and can be aromatic, dihydro or tetrahydro) unsubstituted or substituted with any substituents being selected from the group consisting of OH, OCH.sub.3, CH(CH.sub.3).sub.2, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.3-6 cycloalkyl, CN, NO.sub.2, OCF.sub.3, CF.sub.3, CH.sub.2 CF.sub.3, (CH.sub.2).sub.n CO.sub.2 R.sub.1, and O--(CH.sub.2).sub.n CO.sub.2 R.sub.1 is provided.

TI **Calcilytic** compounds

AB . . . halo, CF.sub.3, OCF.sub.3 and NO.sub.2 ; wherein R represents H, C.sub.1-4 alkyl, and C.sub.3-6 cycloalkyl; and A is phenyl or **naphthyl**, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4. . .

SUMM The present invention relates to novel **calcilytic** compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.

SUMM Various compounds are known to mimic the effects of extra-cellular Ca.sup.2+ on a calcium receptor molecule. **Calcilytics** are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM A is phenyl or **naphthyl**, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4. . .

SUMM . . . to synthesize many of the compounds is described in Schemes 1 and 2. Boc-2-carboxymorpholine can be coupled with the appropriate **amine** such as 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine under

standard conditions such as formation of the corresponding acid fluoride with cyanuric fluoride. Removal of the. . . can be reacted with an appropriately substituted arylfluoride such as 4-fluoro-3-nitro-1-trifluoromethylbenzene, to obtain the corresponding arylamine. Alternatively (scheme 2), the **amine** can be alkylated by reacting with the appropriate alkyl halide or by reaction with the corresponding aldehyde under standard reductive amination conditions. Reduction of the amide bond to the **amine** with BH.sub.3.SMe.sub.2 can then lead to the final products. ##STR3##
##STR4##

- DETD . . . mixture was stirred for 2 h at RT. The reaction mixture was concentrated to dryness in vacuo then diluted with **ethyl** acetate and washed with water. The organic layers were dried (MgSO.sub.4) and the solvent was evaporated to yield a colorless. . .
- DETD The Boc protected **amine** from 1b (1.3 g, 3.3 mmol) was treated with 5 mL of 4M HCl solution in dioxane for 30 min.. . .
- DETD The free **amine** from Example 1b (200 mg, 0.6 mmol), 2-fluoro-1-nitro-5-trifluoromethylphenyl (136 mg, 0.66 mmol) and DIEA (157 mg, 1.2 mmol) were dissolved. . . was heated to reflux for 2 h. After cooling to RT, the solvent was eliminated the residue was dissolved in **Ethyl** Acetate, washed with water. The organic layer was dried (MgSO.sub.4) and the solvent was evaporated to yield a yellow liquid that was purified by flash column chromatography (silica gel, 30% **Ethyl** acetate/hexanes) to obtain the title compound as a bright yellow liquid (327 mg, 100%). MS (ES) m/e 482.0 [M+H].sup.+
- DETD . . . the reaction mixture was heated to reflux for 30 min. The solvent was evaporated and the residue was dissolved in **ethyl** acetate, washed with NaHCO.sub.3 solution, and brine. The combined organic layers were dried (MgSO.sub.4) and the solvent was evaporated. The. . .
- DETD The **amine** from 1b (500 mg, 1.5 mmol) was dissolved in anhydrous methanol (25 mL) then 2,3-dichlorobenzaldehyde (266 mg, 1.5 mmol) and. . . 1.5 mmol). The reaction mixture was stirred at RT overnight. The solvent was eliminated and the residue was diluted with **ethyl** acetate and washed with water. The combined organic layers were dried (MgSO.sub.4) and the solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 30% **Ethyl** Acetate/hexanes) to yield the title compound as a colorless liquid (300 mg, 82% yield based on recovered starting material). MS. . .
- DETD The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .
- DETD The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .
- DETD . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.
- DETD **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .
- DETD To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .
- DETD A typical reaction mixture contains 2 nM .sup.3 H compound

((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-naphthyl)ethylamine), or .sup.3 H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction. . .

CLM What is claimed is:

- . . . halo, CF.sub.3, OCF.sub.3 and NO.sub.2 ; wherein R represents H, C.sub.1-4 alkyl, and C.sub.3-6 cycloalkyl; and A is phenyl or **naphthyl**, unsubstituted or substituted with any substituents being selected from the group consisting of OH, halo, CO.sub.2 R.sub.1, C.sub.1-4 alkyl, C.sub.1-4. . .
- . . . selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia, malignancy and **osteoporosis**.

6. A method according to claim 5 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 18 OF 26 USPATFULL on STN

AN 2001:48117 USPATFULL

TI Calcium receptor-active compounds

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AI US 1995-546998 19951023 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Geist, Gary; Assistant Examiner: Padmanabhan, Sreeni

CLMN Number of Claims: 46

ECL Exemplary Claim: 1

DRWN 137 Drawing Figure(s); 104 Drawing Page(s)

LN.CNT 3074

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention features compounds able to modulate one or more activities of an inorganic ion receptor and methods for treating diseases or disorders by modulating inorganic ion receptor activity. Preferably, the compound can mimic or block the effect of extracellular Ca.sup.2+ on a calcium receptor.

SUMM where Ar.sub.1 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .

SUMM Ar.sub.2 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .

SUMM Inorganic ion receptor-modulating compound include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are compounds which bind to an inorganic ion receptor and mimic (i.e., evoke or potentiate) the effects of an. . .

SUMM . . . caused by an inorganic ion at an inorganic ion receptor. Preferably, the compound affects one or more calcium receptor activities. **Calcilytics** are ionolytics which block one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.

SUMM Preferably, the compound is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .

SUMM where Ar.sub.3 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .

SUMM Ar.sub.4 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .

SUMM where Ar.sub.5 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .

SUMM Ar.sub.6 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, acetyl, lower alkyl, . . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's". . .

SUMM In another preferred embodiment, the compound is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient. . . .

DETD . . . ion receptor modulating compounds modulate one or more inorganic ion receptor activities. Preferred calcium receptor modulating compounds are calcimimetics and **calcilytics**. Inorganic ion receptor modulating compounds can be identified by screening compounds which are modelled after a compound shown to have. . . .

DETD In another preferred embodiment the calcium receptor modulating compound is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . . .

DETD . . . in a cell having a calcium receptor. However, calcimimetics need not possess all the biological activities of extracellular Ca.sup.2+. Similarly, **calcilytics** need not block all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular Ca.sup.2+ to exert their. . . .

DETD where, Ar.sub.1 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . . CH.sub.2 OH, CONH.sub.2, CN, NO.sub.2, CH.sub.3 CH.sub.2, propyl, isopropyl, butyl, isobutyl, t-butyl, and acetoxy. More preferably, Ar.sub.1 is either a **naphthyl** or a phenyl having 1-5 substituents each independently selected from the group consisting of isopropyl, CH.sub.3 O, CH.sub.3 S, CF.sub.3. . . .

DETD Ar.sub.2 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . . CH.sub.2 OH, CONH.sub.2, CN, NO.sub.2, CH.sub.3 CH.sub.2, propyl, isopropyl, butyl, isobutyl, t-butyl, and acetoxy. More preferably, Ar.sub.2 is either a **naphthyl** or a phenyl having 1-5 substituents each independently selected from the group consisting of isopropyl, CH.sub.3 O, CH.sub.3 S, CF.sub.3. . . .

DETD b. Ar.sub.1 is **Naphthyl** and q is 0

DETD In another preferred embodiment, Ar.sub.2 is **naphthyl**, q is 0, and the compound has the formula: ##STR8##

DETD where Ar.sub.1 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . . CH.sub.2 OH, CONH.sub.2, CN, NO.sub.2, CH.sub.3 CH.sub.2, propyl, isopropyl, butyl, isobutyl, t-butyl, and acetoxy. More preferably, Ar.sub.1 is either a **naphthyl** or a phenyl having 1-5 substituents each independently selected from the group consisting of isopropyl, CH.sub.3 O, CH.sub.3 S, CF.sub.3, . . .

DETD c. Ar.sub.2 is **naphthyl** and q is 2
DETD In another preferred embodiment, Ar.sub.1 is a substituted phenyl, Ar.sub.2 is **naphthyl**, q is 2 and the compound has the formula:
##STR11##

DETD where Ar.sub.3 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .
DETD Ar.sub.4 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .
DETD where Ar.sub.5 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . .
DETD Ar.sub.6 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, acetyl, lower alkyl, . . .

DETD **C. Calcilytics**
DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.
DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.
DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.
DETD . . . compounds 9R, 14U, and 17P were prepared by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxymethylborohydride. Compounds 11Y, 12H, 12K, 12M, 14S, 14T, 16L-O, 17E, 17G, 17J, . . .
DETD Compounds 8J, 8U, 11X, 17M, and 25Y were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .
DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H) mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .
DETD N-(3-(2-Phenyl)propyl)-1-(1-**naphthyl**) ethylamine
DETD (R)-N-(1-(2-**naphthyl**)ethyl)-(R)-1-(1-**naphthyl**)ethylamine hydrochloride
DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetoneaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and ETOH (abs.) (100. . .
DETD N-(4-Isopropylbenzyl)-(R)-1-(1-**naphthyl**)ethylamine hydrochloride
DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . .
DETD N-3-(2-methylphenyl)-1-propyl-(R)-3-methoxy-.alpha.-methylbenzyl **amine** hydrochloride

DETD N-3-(2-chlorophenyl)-1-propyl -(R)-1-(1-naphthyl) ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 11, but using 2-chlorohydrocinnamionitrile and (R)-(+)-1-(1-naphthyl)ethylamine on a 10 mmol scale. Chromatography through silica using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .

DETD (R)-N-(1-(4-methoxyphenyl)ethyl)-(R)-1-(1-naphthyl) ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . [Selectosil, 5 .mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nM; 12% ethyl acetate-88% hexane (elution time 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexanes and ethereal HCl was added. . .

DETD N-(3-chloro-4-methoxybenzyl)-(R)-1-(1-naphthyl) ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), and titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.). . .

DETD (R)-N-(1-(4-Methoxy-3-methylphenyl)ethyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), and titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . .

DETD (R,R)-N-(1-Ethyl-4'-methoxy-3'-chlorophenyl)-1-(1-naphthylethyl) amine

DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-naphthyl)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

DETD . . . ether solution was washed with saturated ammonium chloride (4.times.500 ml), dried over anhydrous magnesium sulfate, filtered and concentrated to afford ethyl m-trifluoromethoxycinnamate as an oil; m/z (rel. int.) 260 (M.sup.+, 19), 232 (16), 215 (100), 187 (21), 101 (28).

DETD The ethyl ester in ethanol (100 ml) was reduced under 60 p.s.i. hydrogen using a catalytic amount (10% by weight) palladium hydroxide. After reduction (2 hr, rt) the reaction was filtered and concentrated to afford ethyl m-trifluoromethoxyhydrocinnamate as an oil; m/z (rel. int.) 262 (M.sup.+, 16), 217 (7), 188 (100), 175 (28), 103 (31), 91 (18),. . .

DETD The saturated ethyl ester was hydrolyzed in a solution of ethanol-10 M sodium hydroxide (1:1) for 16 hr at rt. After this time. . .

DETD In a similar fashion an equal molar amount of 4-(3-trifluoromethoxyphenyl)-2-butanone, (R)-1-(1-naphthyl)ethylamine and 1.25 equivalents titanium(IV) isopropoxide were mixed and the intermediate imine reduced with ethanolic sodium cyanoborohydride. Work-up and repetitive preparative thin-layer chromatography using 5% methanol in chloroform afforded (S,R)-N-[4-(3-trifluoromethoxyphenyl)-2-butyl]-1-(1-naphthyl)ethylamine, 22X; m/z (rel. int.) 387 (M.sup.+, 3), 372 (15), 198 (15), 176 (12), 155 (100), 128 (8), 115 (6), 109 (4), 103 (5), 77 (8) and (R,R)-N-[4-(3-trifluoromethoxyphenyl)-2-butyl]-1-(1-naphthyl)ethylamine, 22Y; m/z (rel. int.) 387 (M.sup.+, 2), 372 (12), 198 (16), 176 (11), 155 (100), 128 (8), 115 (6), 109. . .

DETD In a similar fashion an equal molar amount of 4-(3-trifluoromethylphenyl)-2-butanone, (R)-1-(1-naphthyl)ethylamine and 1.25 equivalents titanium(IV) isopropoxide were mixed and the intermediate imine reduced with ethanolic sodium

cyanoborohydride. Work-up and repetitive preparative thin-layer chromatography using 5% methanol in chloroform afforded (S,R)-N-[4-(3-trifluoromethylphenyl)-2-butyl]-1-(1-naphthyl)ethylamine, 25C [m/z (rel. int.) 371 (M.sup.+, 3), 356 (16), 198 (15), 155 (100), 129 (8), 115 (5), 109 (3), 77 (2)] and (R,R)-N-[4-(3-trifluoromethylphenyl)-2-butyl]-1-(1-naphthyl)ethylamine, 25D; m/z (rel. int.) 371 (M.sup.+, 3), 356 (16), 198 (15), 155 (100), 129 (8), 115 (5), 109 (3), 77. . .

DETD In a similar fashion an equal molar amount of 4-phenyl-2-butanone (Aldrich Chemical Co.), (R)-1-(1-naphthyl)ethylamine and 1.25 equivalents titanium(IV) isopropoxide were mixed and the intermediate imine reduced with ethanolic sodium cyanoborohydride. Work-up and repetitive preparative thin-layer chromatography using 5% methanol in chloroform afforded (R,R)-N-(4-phenyl-2-butyl)-1-(1-naphthyl)ethylamine, 21F; m/z (rel. int.) 303 (M.sup.+, 6), 288 (14), 198 (22), 155 (100), 129 (8), 115 (5), 91 (19), 77. . .

DETD . . . 10 mmol). The reaction was stirred 1 hr at rt, cooled to -78.degree. C. and treated with a solution of 1-(1-naphthyl)ethylamine (1.71 g, 10 mmol) in dichloromethane (25 ml). The reaction was transferred to an ice bath and stirred 2 hr.. . . of this material through silica gel using a gradient of chloroform to 10% methanol-chloroform afforded 2.34 g (72% yield) of (R)-N-[3-(2-chlorophenyl)propyl]-1-(1-naphthyl)ethylamine, 12Z, as a clear oil; m/z (rel. int.) 323 (M.sup.+, 2), 308 (63), 288 (7), 196 (5), 184 (5), 155. . .

DETD . . . the intermediate imine treated with an ethanolic sodium cyanoborohydride (5 ml of 1 M, 5 mmol). Work-up and chromatography afforded (R)-N-[1-(4-t-butylphenyl)ethyl]-1-(1-naphthyl)ethylamine, 20A, as an oil; m/z (rel. int.) 331 (M.sup.+, 12), 316 (29), 161 (70), 155 (100), 131 (14), 127 (13),.. . .

DETD . . . the intermediate imine treated with an ethanolic sodium cyanoborohydride (5 ml of 1 M, 5 mmol). Work-up and chromatography afforded (R,R)-N-[1-(4-methoxyphenyl)ethyl]-1-(3-methoxyphenyl)ethylamine, 16L, as an oil; m/z (rel. int.) 284 (M-1, 1), 270 (85), 150 (83), 135 (100), 120 (12), 105 (28), 91 (25), 77 (23) and (S,R)-N-[1-(4-methoxyphenyl)ethyl]-1-(3-methoxyphenyl)ethylamine, 16M, as an oil; m/z (rel. int.) 284 (M-1, 1), 270 (53), 150 (98), 135 (100), 120 (11), 105 (33), 91 (25),.. . .

DETD. . . catalytically reduced (palladium hydroxide, acetic acid, 60 p.s.i. hydrogen 2 hr) to generate 3-methyl-3-(4-chlorophenyl)propylamine. An equal molar amount of the amine, 3'-methoxyacetophenone and 1.25 molar equivalents titanium(IV) isopropoxide were mixed 4 hr at rt and the intermediate imine treated with an. . .

DETD . . . catalytically reduced (palladium hydroxide, acetic acid, 60 p.s.i. hydrogen 2 hr) to generate 3-methyl-3-(3-chlorophenyl)propylamine. An equal molar amount of the amine, 3'-methoxyacetophenone and 1.25 molar equivalents titanium(IV) isopropoxide were mixed 4 hr at rt and the intermediate imine treated with an. . .

DETD . . . catalytically reduced (palladium hydroxide, acetic acid, 60 p.s.i. hydrogen 2 hr) to generate 3-methyl-3-(2-chlorophenyl)propylamine. An equal molar amount of the amine, 3'-methoxyacetophenone and 1.25 molar equivalents titanium(IV) isopropoxide were mixed 4 hr at rt and the intermediate imine treated with an. . .

DETD . . . in diethyl ether and filtered through a 0.45 .mu.M CR PTFE Acrodisc. The diethyl ether filtrate was concentrated to afford N-(3,3-diphenylpropyl)-(1-naphthyl)ethylamine, 3U, as a clear, colorless oil; m/z (rel. int.) 365 (M.sup.+, 17), 350 (19), 181 (23), 155 (100), 141 (25), 115 (11),.. . .

DETD . . . (1.70 g, 10 mmol) and 1.25 equivalents of titanium(IV)

isopropoxide (3.55 g, 12.5 mmol) were treated as above. Work-up yielded N-[1-(2-**naphthyl**)**ethyl**]-1-(3-methoxyphenyl)ethylamine, 6F, as a clear, colorless oil; m/z (rel. int.) 305 (M.sup.+, 1), 290 (35), 170 (49), 155 (100), 135 (55),. . .

DETD . . . of titanium(IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded N-[1-(1-**naphthyl**)**ethyl**]-1-phenylethylamine, 4G, as a clear, colorless oil; m/z (rel. int.) 275 (M.sup.+, 16), 260 (79), 155 (100), 127 (27), 105 (70),.

DETD . . . of titanium(IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded N-[1-(2-**naphthyl**)**ethyl**]-1-phenylethylamine, 4H, as a clear, colorless oil; m/z (rel. int.) 275 (M.sup.+, 1), 260 (61), 155 (100), 120 (36), 105 (55),.

DETD . . . of titanium(IV) isopropoxide were mixed and the resulting intermediate imine was reduced with ethanolic sodium cyanoborohydride. Work-up and chromatography yielded N-1-(1-**naphthyl**)**ethyl**-1-(3-methoxyphenyl)ethylamine, 6E, as a clear, colorless oil; m/z (rel. int.) 305 (M.sup.+, 10), 290 (30), 170 (43), 155 (100), 135 (69),. . .

CLM What is claimed is:

1. A compound having the formula: ##STR15## wherein Ar.sub.5 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen,. . .

3. A compound selected from the group consisting of: 21S ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-propoxyphenyl)ethylamine); 21T ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isopropoxyphenyl)ethylamine); 21U ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isobutoxyphenyl)ethylamine); 21Y ((R,R)-N-(4-(3-(trifluoromethyl)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 22J ((R)-N-(3-(3-(trifluoromethyl)phenyl)propyl)-1-(1-**naphthyl**)ethylamine); 23A ((R)-N-(4-(3-(trifluoromethoxy)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 23E ((R)-N-((3-(trifluoromethoxy)phenyl)methyl)-1-(1-**naphthyl**)ethylamine); 24B (N-((3-methyl-4-methoxyphenyl)methyl)-1-(2-(trifluoromethyl)phenyl)ethylamine); 24J ((R)-N-(3-(3-(trifluoromethoxy)phenyl)propyl)-1-(1-**naphthyl**)ethylamine); 24M ((R)-N-(3-(3,5-difluorophenyl)propyl)-1-(3-methoxyphenyl)ethylamine); 24V (N-((3-methyl-4-methoxyphenyl)methyl)-1-(3-ethylacetoxyphenyl)ethylamine); 24X ((R)-N-((3-bromo-4-methoxyphenyl)methyl)-1-(1-**naphthyl**)ethylamine); 24Y ((R)-N-((3-chloro-4-ethoxyphenyl)methyl)-1-(1-**naphthyl**)ethylamine); 25C ((S,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-**naphthyl**)ethylamine); 25D ((R,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-**naphthyl**)ethylamine); and 25E ((R)-N-(3-phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamine: or a pharmaceutically acceptable salt or complex thereof.

5. The compound of claim 3, wherein said compound is 22J ((R)-N-(3-(3-(trifluoromethyl)phenyl)propyl)-1-(1-**naphthyl**)ethylamine) or a pharmaceutically acceptable salt or complex thereof.

7. The compound of claim 3, wherein said compound is 25D ((R,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-**naphthyl**)ethylamine) or a pharmaceutically acceptable salt or complex thereof.

. . . effective amount of a compound selected from the group consisting of: 21S ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-propoxyphenyl)ethylamine); 21T ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isopropoxyphenyl)ethylamine); 21U ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isobutoxyphenyl)ethylamine);

21Y ((R,R)-N-(4-(3-(trifluoromethyl)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 22J ((R)-N-(3-(3-(trifluoromethyl)phenyl)propyl)-1-(1-naphthyl)ethylamine); 23A ((R)-N-(4-(3-(trifluoromethoxy)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 23E ((R)-N-((3-(trifluoromethoxy)phenyl)methyl)-1-(1-naphthyl)ethylamine); 24B (N-((3-methyl-4-methoxyphenyl)methyl)-1-(2-(trifluoromethyl)phenyl)ethylamine); 24J ((R)-N-(3-(3-(trifluoromethoxy)phenyl)propyl)-1-(1-naphthyl)ethylamine); 24M ((R)-N-(3-(3,5-difluorophenyl)propyl)-1-(3-methoxyphenyl)ethylamine); 24V (N-((3-methyl-4-methoxyphenyl)methyl)-1-(3-(ethylacetoxyl)phenyl)ethylamine); 24X ((R)-N-((3-bromo-4-methoxyphenyl)methyl)-1-(1-naphthyl)ethylamine); 24Y ((R)-N-((3-chloro-4-ethoxyphenyl)methyl)-1-(1-naphthyl)ethylamine); 25C ((S,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-naphthyl)ethylamine); 25D ((R,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-naphthyl)ethylamine); and 25E ((R)-N-(3-phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamine; or a pharmaceutically acceptable salt or complex thereof.

9. A compound having the formula: ##STR16## wherein Ar.sub.3 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of, lower alkyl, halogen, . . . CH.sub.2 OH, CONH.sub.2, CN, acetoxyl, benzyl, benzyloxy, dimethylbenzyl, NO.sub.2, CHO, CH.sub.3 CH(OH), N(CH.sub.3).sub.2, acetyl, and ethylene dioxy; Ar.sub.4 is either **naphthyl** or phenyl optionally substituted with 0 to 5 substituents each independently selected from the group consisting of lower alkyl, halogen, . . .

15. The compound of claim 3, wherein said compound is 23E ((R)-N-((3-(trifluoromethoxy)phenyl)methyl)-1-(1-naphthyl)ethylamine or a pharmaceutically acceptable salt or complex thereof.

16. The compound of claim 3, wherein said compound is 24J ((R)-N-(3-(3-(trifluoromethoxy)phenyl)propyl)-1-(1-naphthyl)ethylamine or a pharmaceutically acceptable salt or complex thereof.

18. The compound of claim 3, wherein said compound is 24X ((R)-N-((3-bromo-4-methoxyphenyl)methyl)-1-(1-naphthyl)ethylamine)) or a pharmaceutically acceptable salt or complex thereof.

19. The compound of claim 3, wherein said compound is 24Y ((R)-N-((3-chloro-4-ethoxyphenyl)methyl)-1-(1-naphthyl)ethylamine or a pharmaceutically acceptable salt or complex thereof.

. . . effective amount of a compound selected from the group consisting of: 21S ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-propoxyphenyl)ethylamine); 21T ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isopropoxyphenyl)ethylamine); 21U ((R)-N-(3-(2-chlorophenyl)propyl)-1-(3-isobutoxyphenyl)ethylamine); 21Y ((R)-N-(4-(3-(trifluoromethyl)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 22J ((R)-N-(3-(3-(trifluoromethyl)phenyl)propyl)-1-(1-naphthyl)ethylamine); 23A ((R)-N-(4-(3-(trifluoromethoxy)phenyl)-2-butyl)-1-(3-methoxyphenyl)ethylamine); 23E ((R)-N-((3-(trifluoromethoxy)phenyl)methyl)-1-(1-naphthyl)ethylamine); 24B (N-((3-methyl-4-methoxyphenyl)methyl)-1-(2-(trifluoromethyl)phenyl)ethylamine); 24J ((R)-N-(3-(3-(trifluoromethoxy)phenyl)propyl)-1-(1-naphthyl)ethylamine); 24M ((R)-N-(3-(3,5-difluorophenyl)propyl)-1-(3-methoxyphenyl)ethylamine); 24V (N-((3-methyl-4-methoxyphenyl)methyl)-1-(3-(ethylacetoxyl)phenyl)ethylamine); 24X ((R)-N-((3-bromo-4-methoxyphenyl)methyl)-1-(1-naphthyl)ethylamine); 24Y ((R)-N-((3-chloro-4-ethoxyphenyl)methyl)-1-(1-naphthyl)ethylamine); 25C ((S,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-

naphthyl)ethylamine); and 25D ((R,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-naphthyl)ethylamine);
25E ((R)-N-(3-phenylprop-2-en-1-yl)-1-(3-methoxyphenyl)ethylamine or a pharmaceutically acceptable salt or complex thereof.

26. The method of claim 21, wherein said compound is 22J
((R)-N-(3-(3-(trifluoromethyl)phenyl)propyl)-1-(1-naphthyl)
ethylamine) or a pharmaceutically acceptable salt or complex thereof.

28. The method of claim 21, wherein said compound is 23E
((R)-N-(3-(3-(trifluoromethoxy)phenyl)methyl)-1-(1-naphthyl)
ethylamine or a pharmaceutically acceptable salt or complex thereof.

. . . method of treating a patient having a disease selected from the group consisting of hyperparathyroidism, Paget's disease, a hypercalcemic disorder, **osteoporosis**, hypertension, and renal osteodystrophy, comprising the step of administering to said patient an effective amount of the compound of any. . .

33. The method of claim 30, wherein said disease is **osteoporosis**

36. The method of claim 21, wherein said compound is 24J
((R)-N-(3-(3-(trifluoromethoxy)phenyl)propyl)-1-(1-naphthyl)
ethylamine or a pharmaceutically acceptable salt or complex thereof.

39. The method of claim 21, wherein said compound is 24X
((R)-N-(3-(3-bromo-4-methoxyphenyl)methyl)-1-(1-naphthyl)
ethylamine) or a pharmaceutically acceptable salt or complex thereof.

40. The method of claim 21, wherein said compound is 24Y
((R)-N-(3-(3-chloro-4-ethoxyphenyl)methyl)-1-(1-naphthyl)
ethylamine or a pharmaceutically acceptable salt or complex thereof.

41. The method of claim 21, wherein said compound is 25C
((S,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-naphthyl)
ethylamine) or a pharmaceutically acceptable salt or complex thereof.

42. The method of claim 21, wherein said compound is 25D
((R,R)-N-(4-(3-trifluoromethyl)phenyl)-2-butyl)-1-(1-naphthyl)
ethylamine) or a pharmaceutically acceptable salt or complex thereof.

46. The compound of claim 9, wherein Ar.sub.3 is either **naphthyl** optionally substituted with 0-5 substituents or phenyl optionally substituted with 1 to 5 substituents each independently selected from the group. . .

L2 ANSWER 19 OF 26 USPATFULL on STN
AN 2000:24677 USPATFULL
TI Calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
DelMar, Eric G., Salt Lake City, UT, United States
Moe, Scott T., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
The Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)
PI US 6031003 20000229
AI US 1995-484719 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994
which is a continuation-in-part of Ser. No. WO 1994-US12117, filed on 21

Oct 1994 Ser. No. Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Borin, Michael

LREP Lyon & Lyon LLP

CLMN Number of Claims: 145

ECL Exemplary Claim: 1

DRWN 109 Drawing Figure(s); 85 Drawing Page(s)

LN.CNT 8955

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.

SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;

SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.

SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.

SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably

thiomethyl. Preferred substituents for R.sub.3. . .

SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.

SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .

SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's. . .

SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .

SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . . .

SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a. . . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium receptor, but not. . . .

SUMM . . . a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . . .

SUMM . . . a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM . . . 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM . . . are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM . . . calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular Ca.sup.2+ on [Ca.sup.2+]sub.i in bovine parathyroid cells ("the **calcilytic** bovine parathyroid cell assay"). Cells were initially bathed in buffer containing 0.5 mM CaCl.sub.2 and, where indicated, the [Ca.sup.2+]sub.i. . . .

DETD . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca.sup.2+ receptors.

DETD . . . agents are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of Ca.sup.2+ at calcium receptors can be determined using procedures. . . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular Ca^{2+} . In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP.

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular Ca^{2+} in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the EC₅₀ or IC₅₀, the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca^{2+} , the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD . . . preferably ##STR7## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp² or preferably sp³ hybridization) Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD . . . ##STR8## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp² or preferably sp³ hybridization). Ar₁=(preferably) phenyl or 2-**naphthyl**; Ar₂ (preferably)=phenyl or 1-**naphthyl**. R₁=(preferably)methyl, R₂=(preferably) H ##STR9## X=nothing; for

example when C (Carbon, see Z=) are sp² or sp^{sup.1}, or for. . .

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-naphthyl, 2-naphthyl, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . .

DETD . . . A. Nelson and Thomas E. D'Ambra in U.S. patent application Ser. No. 276,214, issued as U.S. Pat. No. 5,504,253, entitled "**Amine Preparation**" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR11## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of

amine (1) (typically a primary amine) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary amine may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . . .

DETD . . . the addition of about 500 μ l water. The reaction mixture is then diluted to about 4 ml total volume with ethyl ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, osteoporosis, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . $\text{Ca}_{\text{sup.2+}}$ from intracellular stores; and using fluorescent $\text{Ca}_{\text{sup.2+}}$ indicators. Expression assays can also be used to measure the calcimimetic and calcilytic activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for osteoporosis. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and osteoporosis.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, osteoporosis is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a calcilytic active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from osteoporosis.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from osteoporosis.

DETD Ionomimetics and ionolytics, such as calcimimetics and calcilytics can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or. . . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or calcilytic determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . . .

DETD Screening for Calcimimetic and Calcilytic Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for osteoporosis. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of osteoporosis.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of osteoporosis.

DETD Calcilytic Activity of NPS 021 on Parathyroid Cells

DETD For a compound to be considered a calcilytic, it must block the effects of extracellular $\text{Ca}_{\text{sup.2+}}$ or a calcimimetic compound on an extracellular $\text{Ca}_{\text{sup.2+}}$ -sensing cell. An example of a calcilytic compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . .

. itself cause any change in $[Ca^{sup.2+}]_{sub.i}$ when tested at low $[Ca^{sup.2+}]$ (0.5 mM; FIG. 37). $Ga^{sup.3+}$ is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: $Ga^{sup.3+}$ by itself has no effect on the $Cl^{sup.-}$ currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic component of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular $Ca^{sup.2+}$. . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxymethylborohydride. It was found for the syntheses of these three compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H)-mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of

sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**)ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . .

DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . .

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamionitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . chromatographed [Selectosil, 5-.mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. . .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . .

DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . .

DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1(1-**naphthylethyl**)**amine**

DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

CLM What is claimed is:

. . . (Ca.sup.2+).sub.i in bovine parathyroid cells loaded with fura-2 using the cytosolic Ca.sup.2+ cell assay, and if said compound is a **calcilytic** compound, then said **calcilytic** compound has an IC.sub.50 less than or equal to 5 .mu.M as determined by the **calcilytic** bovine parathyroid cell assay, wherein said compound is not protamine.

3. The method of claim 1 wherein said patient is treated using said **calcilytic** compound.

. . . of aromatic or cycloaliphatic ring or ring system; each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; Y.

4 wherein said hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

7. The method of claim 4, wherein said calcimimetic compound has the formula: ##STR18## and R is H, CH₃, **ethyl**, or isopropyl; or a pharmaceutically acceptable salt thereof.

15. The method of claim 3, wherein said method is used to treat a patient having **osteoporosis**.

31. A method of treating a patient having a disease or disorder which may be treated by a compound which . . . methylene dioxy; each Ar is independently selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy; each R is independently selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; . . .

CH₃ CH₂; each Ar is independently selected from the group consisting of phenyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy; and each R is independently selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, isobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl.

34. The method of claims 31 or 32, wherein each Ar is independently either phenoxy, phenyl, or 1- or 2-**naphthyl**.

35. The method of claim 34, wherein said disease or disorder is selected from the group consisting of hyperparathyroidism, Paget's disease, and **osteoporosis**.

36. The method of claim 35, wherein each Ar is independently either phenyl, or 1- or 2-**naphthyl**.

39. The method of claim 36, wherein said disease or disorder is **osteoporosis**.

41. The method of claim 40, wherein R₁ is lower alkyl of from 1 to 3 carbon atoms; and R₂ is either **naphthyl** or a substituted phenyl having 1 to 5 substituents, and R₃ is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents, wherein each R₂ and R₃ substituent is independently selected from . . .

is 1 to 6 carbon atoms; R₁ is lower alkyl of from 1 to 3 carbon atoms; R₂ is either **naphthyl** or a substituted phenyl having 1 to 5 substituents each independently selected from the group consisting of: lower alkyl of . . . of 1 to 3 carbon atoms, and lower thioalkyl of 1 to 3 carbon atoms; and R₃ is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents each independently selected from the group consisting of: lower alkyl. . .

50. The method of claim 44, wherein R₃ is **naphthyl**.

52. The method of claim 51, wherein R₂ is **naphthyl**.

85. The method of claim 84, comprising administering an effective amount

of a compound of the formula: ##STR28## wherein m. . . of --Cl, --F, --I, --CF.sub.3, --OCF.sub.3 --OCH.sub.2 CF.sub.3, --SCH.sub.3, methyl, isopropyl and methoxy radicals; and R is a hydrogen, methyl, **ethyl**, or isopropyl radical; or a pharmaceutically acceptable salt thereof.

. . . of --Cl, --F, --I, --CF.sub.3, --OCF.sub.3 --OCH.sub.2 CF.sub.3, --SCH.sub.3, methyl, isopropyl and methoxy radicals; and R is a hydrogen, methyl, **ethyl**, or isopropyl radical; or a pharmaceutically acceptable salt thereof.

. . . causing an increase in parathyroid hormone levels comprising the step of administering to said patient an effective amount of a **calcilytic** compound to cause an increase in parathyroid hormone, wherein said **calcilytic** compound decreases one or more activities of a calcium receptor in vitro.

96. A method of treating a patient having a disease or disorder which may be treated by a **calcilytic** compound which decreases one or more activities of a calcium receptor in vitro comprising the step of administering to said patient a therapeutically effective amount of said compound, provided that said patient has Paget's disease or **osteoporosis**.

98. The method of claim 96, wherein said disease or disorder is **osteoporosis**.

99. A method of decreasing parathyroid hormone level in a patient who would benefit from such treatment comprising the step. . . methylene dioxy; each Ar is independently selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy; each R is independently selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; Y. . .

. . . CH.sub.3 CH.sub.2 ; each Ar is independently selected from the group consisting of phenyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy; and each R is independently selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, isobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl.

102. The method of claim 101, wherein each Ar is independently either phenoxy, phenyl, or 1- or 2-**naphthyl**.

105. The method of claim 104, wherein R.sub.1 is lower alkyl of from 1 to 3 carbon atoms; and R.sub.2 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents, and R.sub.3 is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents, wherein each R.sub.2 and R.sub.3 substituent is independently selected from. . .

. . . is 1 to 6 carbon atoms; R.sub.1 is lower alkyl of from 1 to 3 carbon atoms; R.sub.2 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents each independently selected from the group consisting of: lower alkyl of. . . of 1 to 3 carbon atoms, and lower thioalkyl of 1 to 3 carbon atoms; and R.sub.3 is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents each independently selected from the group consisting of: lower alkyl. . .

114. The method of claim 108, wherein R.sub.3 is **naphthyl**.

116. The method of claim 109, wherein R.sub.2 is **naphthyl**.

137. The method of any one of claims 1-3, 4-12, and 27-30, wherein said patient is a human patient and said disease or disorder is **osteoporosis**.

140. The method of claim 132, wherein said disease or disorder is **osteoporosis**.

144. The method of claim 143, wherein alk is straight or branched-chain alkylene of from 1 to 6 carbon atoms; R.sub.1 is lower alkyl of from 1 to 3 carbons; R.sub.2 and R.sub.3 are independently either **naphthyl**, or phenyl optionally substituted with 1 to 5 substituents each independently selected from the group consisting of lower alkyl of. . .

L2 ANSWER 20 OF 26 USPATFULL on STN

AN 2000:15670 USPATFULL

TI Method of using **calcilytic** compounds

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DT Utility

FS Granted

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CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3170

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

TI Method of using **calcilytic** compounds

AB The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic**

compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

SUMM . . . Number WO 94/18959, and Nemeth et al., PCT/US94/12117, International Publication Number WO 95/11211, feature calcium receptor-active molecules and refer to **calcilytics** as compounds able to inhibit calcium receptor activity. For example, WO 94/18959 on page 8, lines 2-13 asserts:

SUMM . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca^{sup.2+} receptors. Such calcimimetics or **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . .

SUMM The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. The ability of a compound to "inhibit calcium receptor activity". . .

SUMM The use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient are described below. Also described below are techniques which can be used to obtain additional **calcilytic** compounds.

SUMM An example of featured **calcilytic** compounds are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives having the chemical formula: ##STR1## where R_{sub.1} is selected from the group consisting. . .

SUMM Preferred **calcilytic** compounds have an IC_{sub.50} .ltoreq.50 .mu.M, more preferably an IC_{sub.50} <10 .mu.M, and even more preferably an IC_{sub.50} <1 .mu.M,. . .

SUMM Patients benefiting from the administration of a therapeutic amount of a **calcilytic** compound can be identified using standard techniques known to those in the medical profession. Diseases or disorders which can be. . .

SUMM Preferably, the **calcilytic** compounds are used to treat diseases or disorders selected from the group consisting of: hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

SUMM . . . invention describes a method of treating a patient comprising the step of administering to the patient an amount of a **calcilytic** compound sufficient to increase serum PTH level. Preferably, the method is carried out by administering an amount of the compound. . .

SUMM Another aspect of the present invention features Structure I **calcilytic** compounds.

SUMM Another aspect of the present invention features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a **calcilytic** compound described herein. The pharmaceutical composition contains the **calcilytic** compound in a form suitable for administration into a mammal, preferably, a human being. Preferably, the pharmaceutical composition contains an amount of a **calcilytic** compound in a proper pharmaceutical dosage form sufficient to exert a therapeutic effect on a human being. However, multiple doses. . .

SUMM . . . or in vitro and is particularly useful to identify those Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives most able to act as **calcilytic** compounds. In vivo assays include measuring a physiological parameter related to calcium receptor activity, such as serum hormone levels or serum calcium ion concentration. In vitro assays include measuring the ability of the **calcilytic** compound to affect intracellular calcium concentration, or cellular hormone secretion. Examples of hormones

levels which can be affected by **calcilytic** compounds include PTH and calcitonin.

SUMM The **calcilytic** compounds described herein can be used as part of in vivo or in vitro methods. Preferably, the compounds are used. . . a patient. Examples of in vitro uses, and other in vivo uses, include use in a method to identify other **calcilytic** compounds and use as a tool to investigate calcium receptor activity or the physiological effects of inhibiting calcium receptor activity. . .

DETD The present application demonstrates the ability of **calcilytic** compounds to exert a physiologically relevant effect on a cell by illustrating the ability of such compounds to increase PTH secretion and also identifies a target site for **calcilytic** compounds. The present application is believed to be the first to demonstrate that **calcilytic** compounds can increase PTH secretion.

DETD Calcium receptors are present on different cell types and can regulate different responses in different cell types. While the **calcilytic** compounds described herein are believed to act at a calcium receptor through a calcium receptor-activity modulating site, unless otherwise explicitly. . . or any particular mode of action. Rather, the present application demonstrates that compounds able to inhibit calcium receptor activity, whose **calcilytic** activity can be measured in vivo or in vitro, exert significant physiological effects. For example, the present application demonstrates the ability of different **calcilytic** compounds to prevent Ca.sup.2+ inhibition of PTH and, thereby, result in an increase in PTH release.

DETD Preferred **calcilytic** compounds described herein are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. Other aspects of the present. . .

DETD **Calcilytic** activity of a compound can be determined using techniques such as those described in the examples below and those described. . .

DETD **Calcilytic** activity varies depending upon the cell type in which the activity is measured. For example, **calcilytic** compounds possess one or more, and preferably all, of the following characteristics when tested on parathyroid cells in vitro:

DETD . . . and cycloalk. Preferably, R.sub.1 is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl, optionally substituted longer-length alkyl, optionally substituted longer-length alkenyl or optionally substituted cycloalk.

DETD More preferably, R.sub.1 is either an optionally substituted phenyl; an optionally substituted **naphthyl**; an optionally substituted pyridyl; an optionally substituted benzothiopyranyl; an optionally substituted carbazole; unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or monosubstituted. . .

DETD . . . Preferably, R.sub.3 and R.sub.4 are each independently a lower alkyl, more preferably, R.sub.3 and R.sub.4 are each independently methyl or **ethyl**;

DETD R.sub.5 is aryl. Preferably, R.sub.5 is either optionally substituted **naphthyl** or optionally substituted phenyl. More preferably, R.sub.5 is substituted phenyl having a substituent in the meta or para position and. . .

DETD . . . substituted. Preferably, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl.

DETD . . . an aryl, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted

naphthyl, or optionally substituted tetrahydronaphthyl. Preferred, R.sub.1 substituents are each independently selected from the group consisting of: unsubstituted alkyl, unsubstituted alkenyl, . . .

DETD More preferred **calcilytic** compounds are Structure I derivatives where R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.6, Z, Y.sub.1 and Y.sub.2 are as described above for. . .

DETD R.sub.5 is either phenyl substituted with one to four independently selected substituents or an optionally substituted **naphthyl** having up to four independently selected substituents. R.sub.5 substituents are provided in Section II, supra., including preferred embodiments. More preferably. . . in a meta or para position, more preferably, the substituent present in a meta or para position is either methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy.

DETD The activity of different **calcilytic** compounds was measured using the Calcium Receptor Assay described below. Examples of compounds having an IC.sub.50 .ltoreq. 50 .mu.M include compounds. . .

DETD R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or. . .

DETD R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or para position selected from the group consisting of: methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position;. . .

DETD The different **calcilytic** compounds described herein can have different stereochemistry around different groups. In an embodiment of the present invention the Structure I. . .

DETD The **calcilytic** compounds described herein can be formulated as a pharmaceutical composition to facilitate the administration of the compound to a patient. Preferred formulations contain a pharmaceutically acceptable carrier and a **calcilytic** compound as described in Section II, supra., including the different embodiments.

DETD . . . effects to patients suffering from a variety of diseases or disorders. Diseases or disorders which can be treated using a **calcilytic** compound are known in the art and can be identified using the present application as a guide. For example, diseases. . .

DETD Diseases and disorders which can be treated using the **calcilytic** compounds described herein include those due to different cellular defects related to calcium receptor activity in different cells, such as. . .

DETD While **calcilytic** compounds of the present invention will typically be used to treat human patients, they may also be used to treat. . .

DETD Preferably, **calcilytic** compounds are used in the treatment of bone and mineral-related diseases or disorders. Bone and mineral-related diseases or disorders comprise. . . and mineral-related diseases or disorders include osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**. More preferably, **calcilytic** compounds are used to treat **osteoporosis**, a disease characterized by reduced bone density and an increased susceptibility to fractures. **Osteoporosis** is associated with aging, especially in women.

DETD One way of treating **osteoporosis** is by altering PTH secretion.

PTH can have a catabolic or an anabolic effect on bone. Whether PTH causes a. . .

DETD As demonstrated by the Examples provided below, **calcilytic** compounds stimulate secretion of PTH. Such **calcilytic** compounds can be used to increase bone formation in a patient, for example, by intermittent dosing, thus achieving intermittent increases.

DETD The **calcilytic** compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical. . .

DETD The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

DETD The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .

DETD This example illustrates the use of the Calcium Receptor Inhibitor Assay. **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

DETD 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

DETD Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives include compounds which have both **calcilytic** activity and .beta.-adrenergic receptor activity. If desired, .beta.-adrenergic activity can be reduced using appropriate functional groups and structural modifications. Modifications. . .

DETD In one embodiment of the present invention the **calcilytic** compounds have an IC.sub.50 .gtoreq.1.0 nM, at the .beta.-adrenergic receptor as measured using the ".beta.-Adrenergic Receptor Binding Assay" described below. In other embodiments, using the .beta.-Adrenergic Receptor Assay **calcilytic** compounds have an IC.sub.50 .gtoreq.1.0 .mu.M, and IC.sub.50 .gtoreq.10.0 .mu.M.

DETD This example illustrates the ability of different **calcilytic** compounds to exert a biological effect on PTH secretion. PTH secretion was determined using dissociated bovine parathyroid cells as described.

DETD . . .

DETD EXAMPLE 4: General Procedures for the Preparation of **Calcilytic** Compounds

DETD The **calcilytic** compounds described by the present invention can be prepared using standard techniques. For example, an overall strategy for preparing preferred. . .

DETD . . . many of the compounds was carried out as follows: A solution of glycidyl ether (i.e., 1,2-epoxy-3-phenoxypropane, 1 mmol) and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, 1.5 mmol) in absolute ethanol (2 mL) is stirred overnight at 50.degree.-60.degree. C. The product is purified by. . .

DETD . . . washed with 10% aqueous NaHCO.sub.3 (3.times.200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Kugelrohr distillation (.about.100 microns) yielded 1-**naphthyl** glycidyl ether as a clear, colorless oil: GC/EI-MS, m/z (rel. int.) 200 (M.sup.+, 61), 184 (1), 169 (5), 157 (12),. . .

DETD A stirred solution of 1-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-fluorophenyl)ethylamine (334 mg, 2 mmol) in absolute ethanol (2 mL) was heated at. . .

DETD . . . mmol) were dissolved in 30 mL of water and enough acetone to

maintain solubility at 0.degree. C. A solution of **ethyl** chloroformate (20.1 g, 185 mmol) in acetone (100 mL) was then added dropwise. An aqueous solution (95 mL) of sodium. . .

DETD Using the method of Example 5, supra, 1-**naphthyl** glycidyl ether (1.0 g, 5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.0 mg, 5.6 mmol) were used to prepare the free base of. . .

DETD EXAMPLE 19: Preparation of N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine. Compound 28 ##STR19##

DETD EXAMPLE 20: Resolution of the Enantiomers (R) and (S)-N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 63 and 64 ##STR20##

DETD The enantiomers (R) and (S)-N-[2-hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine hydrochloride were prepared using the method of Example 7, supra. GC/EI-MS of each enantiomer gave m/z (rel. int.) 366 (M+1,. . . (21), 115 (11), 100 (4), 71 (21). The hydrochloride salt of each enantiomer was prepared by treatment of the free **amine** in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

DETD Using the method of Example 4, supra, 2-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (358 mg, 2 mmol) were used to prepare the free base of. . .

DETD EXAMPLE 51: Preparation of N-[2-Hydroxy-3-(1-adamantanoxypentyl)-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl amine**. Compound 96 ##STR51##

DETD EXAMPLE 64: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 113 ##STR64##

DETD . . . washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by preparative TLC using **ethyl** acetate/hexane as the elutant. The yield of 1-**ethyl**-1-methyl-2-(4-hydroxyphenyl)nitroethane was 0.21 grams.

DETD . . . a suspension of 40% (wt/wt) potassium fluoride on alumina (0.73 g, 5 mmol) in 3 mL of acetonitrile were added 1-**ethyl**-1-methyl-2-(4-hydroxyphenyl)nitroethane (0.21 g, 1.0 mmol) and iodomethane (0.21 g, 1.5 mmol). The reaction was stirred at room temperature for 4 days. . . with sodium bisulfite, sodium carbonate, and saturated brine, then 10 dried over anhydrous sodium sulfate and concentrated. The yield of 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)nitroethane was 0.183 g.

DETD . . . 5 mL of methanol, followed by the addition of sodium borohydride (0.05 g, 1.2 mmol). After stirring for 5 minutes, 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)nitroethane (0.18 g, 0.807 mmol) in 3 mL of methanol was added, and stirred for 5 minutes. Sodium borohydride (0.11 g,. . . hydroxide. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine was 0.127 grams.

DETD Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.086 g, 0.57 mmol) and 1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine (0.11 g, 0.57 mmol) were used to prepare 90 mg of the title compound as a white solid: GC/EI-MS, m/z,. . .

DETD EXAMPLE 66: Preparation of (R)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl amine** Hydrochloride, Compound 115 ##STR66##

DETD EXAMPLE 67: Preparation of (S)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl amine** Hydrochloride, Compound 116 ##STR67##

DETD EXAMPLE 71: Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-**naphthyl**)ethylamine Hydrochloride, Compound 120 ##STR71##

DETD Using the method of Example 52, *supra*, 2-aminomethylnaphthalene (2.51 g, 16 mmol) was used to prepare 1.9 g of 1,1-dimethyl-2-(2-**naphthyl**)ethylamine.

DETD Using the method of Example 6, *supra*, 1,2-epoxy-3-phenoxypropane (0.163 g, 1.1 mmol) and 1,1-dimethyl-2-(2-**naphthyl**)ethylamine (0.26 g, 1.3 mmol) were used to prepare 243 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (230 mg, 1.5 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free **amine** (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1M HCl/ether, yielded 130 mg of the title compound. . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free **amine** (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1M HCl/ether, yielded 88 mg of a white powder: . . .

DETD EXAMPLE 83: Synthesis of (R/S)-1-[[2,2-dimethyl-(4'-methoxy)phenethyl]]amino-2-hydroxy-4(1'-**naphthyl**)-butane. Compound 162 ##STR83##

DETD . . . CH₃sub.2 Cl₃sub.2 and was extracted with sodium sulfite (aqueous) and NaHCO₃sub.3 (aqueous), dried over MgSO₄sub.4, filtered and evaporated to give 1-[(2-oxoaryl)**ethyl**]-naphthalene (1 g) that was carried without further purification.

DETD A solution of 1-[(2-oxoaryl)**ethyl**]-naphthalene (1 g) and 1,1-dimethyl-2(4-methoxyphenyl)ethylamine (985 mg, 5.5 mmol) in ethanol (25 mL) was heated at reflux for 12 hours. . . addition of ether, crystals formed and were subsequently collected and dried in a vacuum oven to give 1.4 g of (R/S)-1-[[2,2-dimethyl-(4'-methoxy)-phenethyl]]amino-2-hydroxy-4(1'-**naphthyl**)-butane. ESMS [(M+H)⁺ = 378, ¹H NMR (CDCl₃, 360MHz) @300.degree. K. .delta. 8.06 (1H, d of d), 7.83 (1H, d of . . .

DETD EXAMPLE 86: N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)**ethyl**]**amine** hydrochloride salt Compound 165 ##STR86##

DETD e) N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)**ethyl**]**amine** hydrochloride salt.

DETD Compound 92: N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(1-**naphthyl**)ethylamine.

CLM What is claimed is:

. . . A method of treating a patient comprising the step of administering to said patient a therapeutically effective amount of a **calcilytic** compound having the formula: ##STR87## wherein R_{sub.1} is selected from the group consisting of: aryl, longer-length alk, and cycloalk; R_{sub.2}. . .

. . . selected from the group consisting of: osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

4. The method of claim 3, wherein disease or disorder is **osteoporosis**.

5. A method of treating a patient comprising the step of administering to said patient an amount of a **calcilytic** compound sufficient to increase serum PTH level, said compound having the formula: ##STR88## wherein R_{sub.1} is selected from the group. . .

. . . The method of any one of claims 1-12, wherein R_{sub.5} is either an optionally substituted phenyl or an optionally substituted **naphthyl**.

17. The method of claim 16, wherein Z is O or methylene, R_{sub.2} is OH,

R.sub.3 is methyl or **ethyl**; and R.sub.4 is methyl or **ethyl**.

24. The method of claim 17, wherein R.sub.5 is a substituted **naphthyl** having one to four substituents each independently selected from the group consisting of: alkoxy, lower-haloalkyl, S-lower alkyl, lower-haloalkoxy, lower alkyl, . . .

26. The method of claim 17, wherein R.sub.5 is **naphthyl**.

30. The method of claim 14, wherein said compound is selected from the group consisting of: (R)-N-(2-hydroxy-3-(3-chloro-2-cyanophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine; (R)-N-(2-hydroxy-3-((2,3-dichloro-4-dipropylsulfamoyl)phenoxy)-1-propyl)-N-(1,1-dimethyl-2-(4-methoxyphenyl)**ethyl**)amine; N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-**naphthyl**)ethylamine; (R)-N-(2-hydroxy-3-(2,3-dichlorophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine; (R)-N-(2-hydroxy-3-(2-cyanophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine; and N-(2-hydroxy-3-(2-nitrophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine; or a pharmaceutically acceptable salt or complex thereof.

L2 ANSWER 21 OF 26 USPATFULL on STN
AN 2000:1911 USPATFULL
TI Calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
DelMar, Eric G., Salt Lake City, UT, United States
Moe, Scott T., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
The Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)
PI US 6011068 20000104
AI US 1994-353784 19941208 (8)
RLI Continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994
And a continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned And a continuation-in-part of Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Lyon & Lyon LLP
CLMN Number of Claims: 103
ECL Exemplary Claim: 1
DRWN 111 Drawing Figure(s); 85 Drawing Page(s)
LN.CNT 7466
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sup.2+ and the

effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

- SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .
- SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.
- SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;
- SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.
- SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.
- SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.
- SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . .
- SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.
- SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .
- SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . .
- SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's. . .
- SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .
- SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . .
- SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for

an ability to mimic or block an activity of extracellular Ca^{2+} on a cell. . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca^{2+} at a first type of calcium receptor, but not. . .

SUMM . . . a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . .

SUMM . . . a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**. . .

SUMM . . . 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor. . .

SUMM . . . are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds. . .

SUMM . . . calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**. . .

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular Ca^{2+} on $[\text{Ca}^{2+}]_{\text{sub.i}}$ in bovine parathyroid cells. Cells were initially bathed in. . .

DETD . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca^{2+} receptors. . .

DETD . . . are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of Ca^{2+} at calcium receptors can be determined using procedures. . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular Ca^{2+} . In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques. . .

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP. . .

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular Ca^{2+} in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the EC_{50} or IC_{50} , the more potent the molecule as a calcimimetic or **calcilytic**. . .

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion

are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca^{2+} , the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD . . . Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp.² or preferably sp.³ hybridization) Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD Ar.¹=(preferably) phenyl or 2-**naphthyl**; Ar2 (preferably)=phenyl or 1-**naphthyl**. R.¹=(preferably) methyl, R.² -(preferably)H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-**naphthyl**, 2-**naphthyl**, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-tiazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . . .

DETD . . . A. Nelson and Thomas E. D'Ambra in U.S. patent application Ser. No. 276,214 issued as U.S. Pat. No. 5,504,253 entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and

nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a DOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or

indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or . . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic** Activity of NPS 021 on Parathyroid Cells

DETD For a compound to be considered a **calcilytic**, it must block the effects of extracellular $\text{Ca}_{\text{sup.2+}}$ or a calcimimetic compound on an extracellular $\text{Ca}_{\text{sup.2+}}$ -sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}_{\text{sup.2+}}]_{\text{sub.i}}$ when tested at low $[\text{Ca}_{\text{sup.2+}}]$ (0.5 mM; FIG. 37). $\text{Ga}_{\text{sup.3+}}$ is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: $\text{Ga}_{\text{sup.3+}}$ by itself has no effect on the $\text{Cl}_{\text{sup.-}}$ currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic components of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular Ca^{2+} . . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride. It was found for the syntheses of these three compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H)-mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride. . .

DETD N-3-Phenyl -1-propyl-1-(1-**naphthyl**) ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)**ethyl**)-1-(1-**naphthyl**) ethylamine hydrochloride

DETD A mixture of (R)-(+)-1(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetoneaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . .

DETD (R)-N -(4-Isopropylbenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV)-isopropoxide (2.2 g, 7.7 mmol) was heated to 100.degree.. . .

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)**ethyl**)-1-(1-**naphthyl**) ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . chromatographed [Selectosil, 5- μ M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. . .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . . .

DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . . .

DETD (R,R)-N-(1-**Ethyl** -4' -methoxy-3'-chlorophenyl)-1(1-**naphthylethyl**)**amine**

DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

CLM What is claimed is:

. . . either n-propylene, 2,4-butylene, or 1,3-butylene; R.sub.1 is a lower alkyl of from 1 to 3 carbon atoms; R.sub.2 is either **naphthyl** or a phenyl substituted with 1 to 5 substituents, and R.sub.3 is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents; wherein each of said R.sub.2 substituents and each of said. . . .

7. The compound of claim 6, wherein R.sub.2 is either **naphthyl** or said phenyl having 1 to 5 substituents; and R.sub.3 is either **naphthyl** or said phenyl optionally substituted with 1 to 5 substituents.

10. The compound of any one of claims 8 or 9, wherein R.sub.3 is **naphthyl**.

12. The compound of claim 11, wherein R.sub.2 is **naphthyl**.

26. A compound represented by a formula selected from the group consisting of ##STR22## wherein m is independently an integer of 0 to 5 for **naphthyl** rings and m is independently an integer of 1 to 5 for phenyl rings; x is independently selected from the. . . .

--CF.sub.2 H, --CFH.sub.2, --CH.sub.2 CF.sub.3 or phenyl radical; provided that if said compound has the chemical formula: ##STR23## wherein the **naphthyl** is either unsubstituted or substituted with a lower alkyl or halogen and only one substituent is present on the phenyl,. . . .

. . . of --Cl, --F, --I, --CF.sub.3, --OCF.sub.3, --OCH.sub.2 CF.sub.3, --SCH.sub.3, methyl, isopropyl and methoxy radicals; and R is a hydrogen, methyl, **ethyl** or isopropyl radical; or a pharmaceutically acceptable acid addition salt or complex thereof.

. . . not contain a OH substituent, and R.sub.3 is not 4-OCH.sub.3 -phenyl, or 4-CH.sub.3 -phenyl, or R.sub.2 is an optionally substituted **naphthyl** and R.sub.3 is a substituted phenyl not containing an OH substituent; and further provided that if one of R.sub.2 or R.sub.3 is **naphthyl** or **naphthyl** substituted with a lower alkyl of 1 to 3 carbons or halogen and the other of R.sub.2 or R.sub.3 is. . . .

39. The compound of claim 38, wherein R.sub.2 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents; and R.sub.3 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents.

42. The compound of claim 41, wherein R.sub.2 is **naphthyl**.

66. The compound of any one of claims 61-65, wherein R.sub.3 is

naphthyl.

68. The compound of claim 67, wherein R.sub.2 is **naphthyl**.

80. The pharmaceutical composition of claim 79, wherein alk is 1 to 6 carbon atoms; R.sub.1 is lower alkyl of from 1 to 3 carbon atoms; and R.sub.2 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents, and R.sub.3 is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents, wherein each R.sub.2 and R.sub.3 substituent is independently selected from. . .
. . . is 1 to 6 carbon atoms; R.sub.1 is lower alkyl of from 1 to 3 carbon atoms; R.sub.2 is either **naphthyl** or a substituted phenyl having 1 to 5 substituents each independently selected from the group consisting of: lower alkyl of. . . of 1 to 3 carbon atoms, and lower thioalkyl of 1 to 3 carbon atoms; and R.sub.3 is either cyclohexyl, **naphthyl**, or a phenyl optionally substituted with 1 to 5 substituents each independently selected from the group consisting of: lower alkyl. . .

89. The pharmaceutical composition of any one of claims 84-88, wherein R.sub.3 is **naphthyl**.

91. The pharmaceutical composition of claim 90, wherein R.sub.2 is **naphthyl**.

L2 ANSWER 22 OF 26 USPATFULL on STN
AN 1999:163739 USPATFULL
TI Calcium receptor-active molecules
IN Nemeth, Edward F., Salt Lake City, UT, United States
Van Wagenen, Bradford C., Salt Lake City, UT, United States
Balandrin, Manuel F., Sandy, UT, United States
Delmar, Eric G., Salt Lake City, UT, United States
Moe, Scott T., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 6001884 19991214
AI US 1995-469204 19950606 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. WO 1994-US12177, filed on 21 Oct 1994 And a continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned And a continuation-in-part of Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And a continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.
LREP Lyon & Lyon LLP
CLMN Number of Claims: 44
ECL Exemplary Claim: 1
DRWN 90 Drawing Figure(s); 90 Drawing Page(s)
LN.CNT 1555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention features molecules which can modulate one or activities of an inorganic ion receptor. Preferably, the molecule can mimic or block the effect of extracellular Ca.sup.2+ on a calcium receptor. The preferred use of such molecules is to treat diseases or

disorders by altering inorganic ion receptor activity, preferably calcium receptor activity.

SUMM . . . affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, **osteoporosis** is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic . . . levels (e.g., a parathyroid cell ionmimetic) can retard bone loss and, thus, result in beneficial effects to patients suffering from **osteoporosis**.

SUMM . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from **osteoporosis**.

SUMM . . . modulates one or more effects of an inorganic ion receptor. Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and **calcilytics**.

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. **Calcilytics** are ionlytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium. . .

SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; and

SUMM In preferred embodiments R is either H, CH.sub.3, **ethyl**, or isopropyl, and each X is independently selected from the group consisting of isopropyl, CH.sub.3 O, CH.sub.3 S, CF.sub.3 O, . . .

SUMM . . . preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's. . .

SUMM . . . C-cells. Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DETD . . . mimic or block an effect of extracellular Ca.sup.2+ on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and **calcilytics**. Generic and specific structures of inorganic ion receptor modulating agents are provided in the Summary supra, and in FIG. 1.

DETD Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .

DETD In another preferred embodiment the calcium receptor modulating agent is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . .

DETD . . . need not possess all the biological activities of extracellular Ca.sup.2+, but, rather, at least one such activity is mimicked. Similarly, **calcilytics** need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular Ca.sup.2+ to exert their. . .

DETD **B. Calcilytics**

DETD . . . and 16P are provided below. Compounds 4L, 8J, 8U, 11X and 16M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD . . . compounds 9R, 14U, and 16P were prepared by reductive amination

of a commercially available aldehyde or ketone with a primary amine in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride. It was found for the syntheses of these three compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H) mediated condensation of an amine with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-naphthyl)ethylamine

DETD (R)-N-(1-(2-naphthyl)ethyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . . .

DETD N-(4-Isopropylbenzyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . . .

DETD N-3-(2-chlorophenyl)-1-propyl-(R)-1-(1-naphthyl)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 6, but using 2-chlorohydrocinnamitrile and (R)-(+)-1-(1-naphthyl)ethylamine on a 10 mmol scale. Chromatography through silica using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . . .

DETD (R)-N-(1-(4-methoxyphenyl)ethyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . . [Selectosil, 5 .mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% ethyl acetate-88% hexane (elution time 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexanes and ethereal HCl was added. . . .

DETD N-(3-chloro-4-methoxybenzyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), and titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.). . . .

DETD (R)-N-(1-(4-Methoxy-3-methylphenyl)ethyl)-(R)-1-(1-naphthyl)ethylamine hydrochloride [Compound 16P]

DETD A mixture of (R)-(+)-1-(1-naphthyl)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), and titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . . .

CLM What is claimed is:

- . . . aromatic ring made up of two X or two Y; R is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; and. . . independently between 0 and 5 inclusive; provided that two of X together make up a fused phenyl to form a naphthyl which may be substituted; provided that if R is hydrogen, then Y.sub.n is not 2-hydroxy-3-CH.sub.3 O, 2-hydroxy-3-CH.sub.3 CH.sub.2 O, or. . . .
3. The compound of claim 2 wherein R is selected from the group consisting of H, CH.sub.3, ethyl, and isopropyl.

- . . . together; provided that a fused phenyl made up of two of X together is present to form an optionally substituted naphthyl; R is selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl,

cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; and. . .
. . . a fused aromatic ring made up of two X; and R is selected from the group consisting of H, CH.sub.3, **ethyl**, and isopropyl.

. . . together; provided that a fused phenyl made up of two of X together is present to form an optionally substituted **naphthyl**; R is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, butyl, allyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl; and. . .
. . . and a fused aromatic ring made up of two X; R is selected from the group consisting of H, CH.sub.3, **ethyl**, and isopropyl.

39. The method of any of one of claims 25-34, wherein said method is used to treat **osteoporosis**.

41. A method according to claim 40 wherein said disease or disorder is selected from the group consisting of hyperparathyroidism, **osteoporosis**, gut motility disorders, diarrhea, GI ulcer diseases, GI absorption diseases, sarcoidosis, and autoimmune diseases.

L2 ANSWER 23 OF 26 USPATFULL on STN
AN 1999:121216 USPATFULL
TI Calcium receptor-active molecules
IN Brown, Edward M., Milton, MA, United States
Hebert, Steven C., Wellesley, MA, United States
Garrett, Jr., James E., Salt Lake City, UT, United States
PA NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
Brigham and Women's Hospital, Boston, MA, United States (U.S. corporation)
PI US 5962314 19991005
AI US 1997-943986 19971003 (8)
RLI Continuation of Ser. No. US 1995-484565, filed on 7 Jun 1995, now patented, Pat. No. US 5763569 which is a continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. WO 1994-US12117, filed on 21 Oct 1994 Ser. No. Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Saoud, Christine
LREP Lyon & Lyon LLP
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 111 Drawing Figure(s); 85 Drawing Page(s)
LN.CNT 7882
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca.sup.2+ and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof,

targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

- SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .
- SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.
- SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;
- SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinoliny, 2- or 3-indolyl, benzyl, and phenoxy.
- SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.
- SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.
- SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . .
- SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.
- SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .
- SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . .
- SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's. . .
- SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .
- SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . .
- SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a cell. . .
- SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium

receptor, but not. . .

SUMM . . . a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . .

SUMM . . . a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM . . . 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM . . . are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM . . . calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular $\text{Ca}_{\text{sup.2+}}$ on $[\text{Ca}_{\text{sup.2+}}]_{\text{sub.i}}$ in bovine parathyroid cells. Cells were initially bathed in. . .

DETD . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at $\text{Ca}_{\text{sup.2+}}$ receptors.

DETD . . . agents are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to-mimic or block an activity of $\text{Ca}_{\text{sup.2+}}$ at calcium receptors can be determined using procedures described. . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular $\text{Ca}_{\text{sup.2+}}$. In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP.

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular $\text{Ca}_{\text{sup.2+}}$ in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the $\text{EC}_{\text{sub.50}}$ or $\text{IC}_{\text{sub.50}}$, the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca^{sup.2+}, the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD . . . ##STR6## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp^{sup.2} or preferably sp^{sup.3} hybridization) Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD . . . ##STR7## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp^{sup.2} or preferably sp^{sup.3} hybridization). Ar^{sup.1}=(preferably) phenyl or 2-**naphthyl**; Ar^{sup.2} (preferably)=phenyl or 1-**naphthyl**. R^{sup.1}=(preferably) methyl, R^{sup.2}=(preferably) H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-**naphthyl**, 2-**naphthyl**, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . . .

DETD . . . described by Bradford C Vanwagenen, Steven R Duff, William A. Nelson and Thomas E. D'Ambra in U.S. Patent Application, entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with

di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of

parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or . . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic** Activity of NPS 021 on Parathyroid Cells

DETD For a compound to be considered a **calcilytic**, it must block the effects of extracellular Ca^{2+} or a calcimimetic compound on an extracellular Ca^{2+} - sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}^{2+}]_{\text{sub.i}}$ when tested at low $[\text{Ca}^{2+}]$ (0.5 mM; FIG. 37). Ga^{3+} is also **calcilytic** to Xenopus oocytes expressing the cloned calcium receptor: Ga^{3+} by itself has no effect on the Cl^{+} currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states

where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic components of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular Ca.sup.2+. . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxymorohydride. It was found for the syntheses of these three compounds (9R,. . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H)-mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**)ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetonephthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . .

DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . .

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamionitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)**ethyl**)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.). . . chromatographed [Selectosil, 5-.mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39

mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . . .
DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)**ethyl**)-1-(1-
naphthyl)ethylamine hydrochloride [Compound 17P]
DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8
mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium
(IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . . .
DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1-(1-
naphthylethyl)**amine**
DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol),
(R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium
(IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated
to 100.degree. C.. . . .

L2 ANSWER 24 OF 26 USPATFULL on STN

AN 1999:4350 USPATFULL

TI Method of screening calcium receptor-active molecules

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Aug 1994, now abandoned And a continuation-in-part of Ser. No. US
1993-141248, filed on 22 Oct 1993, now abandoned And a
continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now
abandoned which is a continuation-in-part of Ser. No. US 1993-17127,
filed on 12 Feb 1993, now abandoned which is a continuation-in-part of
Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a
continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992,
now abandoned which is a continuation-in-part of Ser. No. US
1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Walsh, Stephen; Assistant Examiner: Sorensen, Kenneth
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CLMN Number of Claims: 48

ECL Exemplary Claim: 1

DRWN 111 Drawing Figure(s); 85 Drawing Page(s)

LN.CNT 7588

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the different roles inorganic ion
receptors have in cellular and body processes. The present invention
features: (1) molecules which can modulate one or more inorganic ion
receptor activities, preferably the molecule can mimic or block an
effect of an extracellular ion on a cell having an inorganic ion
receptor, more preferably the extracellular ion is Ca.sup.2+ and the
effect is on a cell having a calcium receptor; (2) inorganic ion
receptor proteins and fragments thereof, preferably calcium receptor
proteins and fragments thereof; (3) nucleic acids encoding inorganic ion
receptor proteins and fragments thereof, preferably calcium receptor
proteins and fragments thereof; (4) antibodies and fragments thereof,

targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.

SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;

SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.

SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.

SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . .

SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.

SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .

SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's". . .

SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .

SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . .

SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a cell. . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium

receptor, but not. . . .

SUMM a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . . .

SUMM a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular $\text{Ca}_{\text{sup.2+}}$ on $[\text{Ca}_{\text{sup.2+}}]_{\text{sub.i}}$ in bovine parathyroid cells. Cells were initially bathed in. . . .

DETD can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at $\text{Ca}_{\text{sup.2+}}$ receptors.

DETD agents are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of $\text{Ca}_{\text{sup.2+}}$ at calcium receptors can be determined using procedures. . . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . . .

DETD useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular $\text{Ca}_{\text{sup.2+}}$. In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP. . . .

DETD to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular $\text{Ca}_{\text{sup.2+}}$ in a PMA-sensitive manner, it is. . . . for primary or secondary hyperparathyroidism. The lower the $\text{EC}_{\text{sub.50}}$ or $\text{IC}_{\text{sub.50}}$, the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca.^{sup.2+}, the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD Ar.^{sup.1}=(preferably) phenyl or 2-**naphthyl**; Ar.^{sup.2} (preferably)=phenyl or 1-**naphthyl**. R.^{sup.1}=(preferably) methyl, R.^{sup.2}=(preferably) H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-**naphthyl**, 2-**naphthyl**, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-thiazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . .

DETD . . . described by Bradford C VanWagenen, Steven R Duff, William A. Nelson and Thomas E. D'Ambra in U.S. patent Application, entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in

the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing

with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or. . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic** Activity of NPS 021 on Parathyroid Cells

DETD For a compound to be considered a **calcilytic**, it must block the effects of extracellular Ca^{2+} or a calcimimetic compound on an extracellular Ca^{2+} -sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}^{2+}]_{\text{sub.i}}$ when tested at low $[\text{Ca}^{2+}]_{\text{sub.i}}$ (0.5 mM; FIG. 37). Ga^{3+} is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: Ga^{3+} by itself has no effect on the Cl^{-} currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors.

Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic components of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular Ca^{2+} . . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride. It was found for the syntheses of these three compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H)-mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**) ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . .

DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**) ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . .

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamionitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . chromatographed [Selectosil, 5- μm silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. . .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . .

DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)ethyl)-1-(1-

naphthyl)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . .

DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1-(1-**naphthylethyl**)**amine**

DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

CLM What is claimed is:

. . . comprises a moiety selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

. . . said aromatic group comprises a moiety selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, 1- or 2- **naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

24. The method of claim 22, wherein said aromatic group comprises said 1- or 2- **naphthyl** moiety.

. . . aromatic group is selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy, and said test compound is not verapamil or D-600.

. . . said aromatic group comprises a moiety selected from the group consisting of; phenyl, 2-, 3-, or 4-pyridyl, 1- or 2- **naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

33. The method of claim 31, wherein said aromatic group comprises said 1- or 2- **naphthyl** moiety.

. . . said aromatic group is selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy, and said test compound is not verapamil or D-600.

. . . said aromatic group comprises a moiety selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, 1- or 2- **naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

40. The method of claim 38, wherein said aromatic group comprises said 1- or 2- **naphthyl** moiety.

41. A method of identifying a **calcilytic** compound comprising the steps of: a) contacting a cell comprising a calcium receptor with a test compound; and b) determining. . .

. . . aromatic group is selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-**naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy, and said test compound is not verapamil or D-600.

. . . said aromatic group comprises a moiety selected from the group consisting of: phenyl, 2-, 3-, or 4-pyridyl, 1- or 2- **naphthyl**, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

47. The method of claim 45, wherein said aromatic group comprises said 1- or 2- **naphthyl** moiety.

L2 ANSWER 25 OF 26 USPATFULL on STN
 AN 1998:65348 USPATFULL
 TI Calcium receptor-active molecules
 IN Brown, Edward M., Milton, MA, United States
 Hebert, Steven C., Wellesley, MA, United States
 Garrett, Jr., James E., Salt Lake City, UT, United States
 PA The Brigham and Women's Hospital, Inc, Boston, MA, United States (U.S. corporation)
 NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S. corporation)
 PI US 5763569 19980609
 AI US 1995-484565 19950607 (8)
 RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned, said Ser. No. US -292827 which is a continuation-in-part of Ser. No. US -141248 which is a continuation-in-part of Ser. No. US -9389 And a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Walsh, Stephen; Assistant Examiner: Sorensen, Kenneth A.
 LREP Lyon & Lyon LLP
 CLMN Number of Claims: 13
 ECL Exemplary Claim: 1
 DRWN 111 Drawing Figure(s); 85 Drawing Page(s)
 LN.CNT 6942
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The present invention features calcium receptor polypeptides and fragments thereof. Uses of a calcium receptor polypeptide include providing a polypeptide having the activity of a calcium receptor polypeptide. Calcium receptor polypeptide fragments can be used, for example, to generate antibodies to a calcium receptor polypeptide.
 SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .
 SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.
 SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;
 SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.
 SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.

SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted phenyl or **naphthyl**.

SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . .

SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.

SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . .

SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as "Harrison's. . .

SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . .

SUMM . . . identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . .

SUMM . . . suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a cell. . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium receptor, but not. . .

SUMM . . . a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . .

SUMM . . . a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM . . . 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM . . . are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM . . . calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular Ca.sup.2+ on [Ca.sup.2+]sub.i in bovine parathyroid cells. Cells were initially bathed in. . .

DETD . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful

calcimimetics or **calcilytics** which are active at Ca.sup.2+ receptors.

DETD . . . agents are provided in the Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of Ca.sup.2+ at calcium receptors can be determined using procedures. . . .

DETD **C. Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular Ca.sup.2+. In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP. . . .

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular Ca.sup.2+ in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the EC.sub.50 or IC.sub.50, the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca.sup.2+, the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary amine, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD . . . ##STR6## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or

more preferably branched hydrocarbon (sp.^{sup.2} or preferably sp.^{sup.3} hybridization) Ar=(preferably) phenyl, 1-, or 2-naphthyl

DETD . . . ##STR7## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp.^{sup.2} or preferably sp.^{sup.3} hybridization). Ar.^{sup.1}=(preferably) phenyl or 2-naphthyl; Ar.^{sup.2} (preferably)=phenyl or 1-naphthyl. R.^{sup.1}=(preferably) methyl, R.^{sup.2}=(preferably) H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-naphthyl, 2-naphthyl, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthryl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . .

DETD . . . described by Bradford C VanWagenen, Steven R Duff, William A. Nelson and Thomas E. D'Ambra in U.S. Patent Application, entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on silica gel using combinations. . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic

hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or. . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic Activity of NPS 021 on Parathyroid Cells**
 DETD For a compound to be considered a **calcilytic**, it must block the effects of extracellular Ca^{2+} or a calcimimetic compound on an extracellular Ca^{2+} -sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}^{2+}]_{\text{sub.i}}$ when tested at low $[\text{Ca}^{2+}]$ (0.5 mM; FIG. 37). Ga^{3+} is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: Ga^{3+} by itself has no effect on the Cl^{-} currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic component of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular Ca^{2+} . . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine**

in the presence of sodium cyanoborohydride or sodium triacetoxymethylborohydride. It was found for the syntheses of these three compounds (9R, . . .

- DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H) -mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .
- DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**)ethylamine
- DETD (R,R)-N-(1-(2-**Naphthyl**)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride
- DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.) (100. . .
- DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride
- DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated to. . .
- DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride
- DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . .
- DETD (R,R)-N-(1-(4-Methoxyphenyl)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride
- DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . chromatographed [Selectosil, 5-.mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. . .
- DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride
- DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . .
- DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride [Compound 17P]
- DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.) (1. . .
- DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1-(1-**naphthylethyl**)**amine**
- DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**)ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree. C.. . .

L2 ANSWER 26 OF 26 USPATFULL on STN

AN 97:107219 USPATFULL

TI Calcium receptor-active molecules

IN Brown, Edward M., Milton, MA, United States

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NPS Pharmaceuticals, Inc., Salt Lake City, UT, United States (U.S.

corporation)
PI US 5688938 19971118
AI US 1995-485588 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1994-353784, filed on 8 Dec 1994 which is a continuation-in-part of Ser. No. US 1993-9389, filed on 23 Feb 1993, now abandoned Ser. No. US 1993-141248, filed on 22 Oct 1993, now abandoned And Ser. No. US 1994-292827, filed on 19 Aug 1994, now abandoned which is a continuation-in-part of Ser. No. US -141248 which is a continuation-in-part of Ser. No. US -9389 which is a continuation-in-part of Ser. No. US 1993-17127, filed on 12 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-934161, filed on 21 Aug 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-834044, filed on 11 Feb 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-749451, filed on 23 Aug 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Walsh, Stephen; Assistant Examiner: Sorensen, Kenneth A.

LREP Lyons & Lyons LLP

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 111 Drawing Figure(s); 84 Drawing Page(s)

LN.CNT 6522

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the different roles inorganic ion receptors have in cellular and body processes. The present invention features: (1) molecules which can modulate one or more inorganic ion receptor activities, preferably the molecule can mimic or block an effect of an extracellular ion on a cell having an inorganic ion receptor, more preferably the extracellular ion is Ca^{2+} and the effect is on a cell having a calcium receptor; (2) inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (3) nucleic acids encoding inorganic ion receptor proteins and fragments thereof, preferably calcium receptor proteins and fragments thereof; (4) antibodies and fragments thereof, targeted to inorganic ion receptor proteins, preferably calcium receptor protein; and (5) uses of such molecules, proteins, nucleic acids and antibodies.

SUMM Inorganic ion receptor-modulating agents include ionomimetics, ionolytics, calcimimetics, and **calcilytics**. Ionomimetics are molecules which bind to an inorganic ion receptor and mimics (i.e., evokes or potentiates) the effects of an. . .

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule affects one or more calcium receptor activities. **Calcilytics** are ionolytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and bind to a calcium receptor.

SUMM each R independently is selected from the group consisting of hydrogen, methyl, **ethyl**, propyl, isopropyl, allyl, butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, indenyl, indanyl, dihydroindolyl, thiodihydroindolyl, and 2-, 3-, or 4-piperid(in)yl;

SUMM . . . system. Preferably, the hydrophobic entity is selected from the group consisting of phenyl, cyclohexyl, 2-, 3-, or 4-pyridyl, 1- or 2-**naphthyl**, .alpha.- or .beta.-tetrahydronaphthyl, 1- or 2-quinolinyl, 2- or 3-indolyl, benzyl, and phenoxy.

SUMM . . . of which has aromatic character and include carbocyclic aryl groups such as phenyl and bicyclic carbocyclic aryl groups such as **naphthyl**.

SUMM . . . are compounds where R.sub.1 is R-methyl. Also preferred are those compounds where R.sub.2 and R.sub.3 are optionally substituted

phenyl or **naphthyl**.

SUMM More preferred compounds are those where R.sub.2 is monosubstituted phenyl, more preferably meta-substituted; or 1-**naphthyl**. More preferred R.sub.3 groups are unsubstituted or monosubstituted phenyl, especially meta- or ortho-substituted, or 2-**naphthyl**. Preferred substituents for R.sub.2 are halogen, haloalkyl, preferably trihalomethyl, alkoxy, preferably methoxy, and thioalkyl, preferably thiomethyl. Preferred substituents for R.sub.3. . . .

SUMM R is preferably H, CH.sub.3, **ethyl**, or isopropyl.

SUMM Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 .mu.M, and even more. . . .

SUMM Preferably, the molecule is either a calcimimetic or a **calcilytic** which modulates one or more calcium receptor activity. Examples of calcium receptor-modulating molecules or agents are described herein. Additional calcium. . . .

SUMM Diseases characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis** and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as. "Harrison's. . . .

SUMM In another preferred embodiment, the agent is a **calcilytic** acting on a parathyroid cell calcium receptor and increases the level of parathyroid hormone in the serum of the patient.. . . .

SUMM identify the number and/or location and/or functional integrity of the calcium receptors; the assay involves providing a labeled calcimimetic or **calcilytic** molecule; the presence of a cancer, e.g., an ectopic tumor of the parathyroid, is tested for by measuring calcium receptor. . . .

SUMM suffering from a disease characterized by an abnormal inorganic ion activity. Preferably, the method is used to identify calcimimetics or **calcilytics** by screening potentially useful molecules for an ability to mimic or block an activity of extracellular Ca.sup.2+ on a cell. . . .

SUMM Preferably, the activity of molecules in different cells is tested to identify a calcimimetic or **calcilytic** molecule which mimics or blocks one or more activities of Ca.sup.2+ at a first type of calcium receptor, but not. . . .

SUMM a binding site, epitope for antibody recognition (typically at six amino acids), and/or a site which binds a calcimimetic or **calcilytic**. Other preferred receptor fragments include those having only an extracellular portion, a transmembrane portion, an intracellular portion, and/or a multiple. . . .

SUMM a functioning calcium receptor. Cells containing a functioning calcium receptor can be used, for example, to screen for calcimimetics or **calcilytics**.

SUMM 7 or SEQ. ID. NO. 8. Other binding agents include molecules which bind to the receptor, for example, calcimimetics and **calcilytics** binding to the calcium receptor.

SUMM are useful to elucidate which portion of the receptor a particular molecule such as the natural ligand, a calcimimetic, or **calcilytic**, binds.

SUMM calcitonin from C-cells. Such molecules can be used to treat diseases characterized by abnormal calcium homeostasis such as hyperparathyroidism and **osteoporosis**.

DRWD FIGS. 37a and 37b are graphical representations showing that NPS 021 is a **calcilytic** compound that blocks the effects of extracellular Ca.sup.2+ on [Ca.sup.2+].sub.i in bovine parathyroid cells. Cells were initially bathed in. . . .

DETD can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca.sup.2+ receptors.

DETD . . . agents are provided in the. Summary supra, and in FIGS. 1 and 36. Preferred calcium receptor-modulating agents are calcimimetics and **calcilytics**. The ability of molecules to mimic or block an activity of Ca.sup.2+ at calcium receptors can be determined using procedures. . .

DETD C. **Calcilytics**

DETD Rational design of calcium receptor-modulating agents involves studying a molecule known to be calcimimetic or **calcilytic** and then modifying the structure of the known molecule. For example, polyamines are potentially calcimimetic since spermine mimics the action. . .

DETD . . . useful to find molecules, including calcimimetic molecules, of this invention. Equivalent procedures can be used to find ionolytic molecules, including **calcilytic** molecules, by screening for those molecules most antagonistic to the actions of the ion, including extracellular Ca.sup.2+ . In vitro assays can be used to characterize the selectivity, saturability, and reversibility of these calcimimetics and **calcilytics** by standard techniques.

DETD Various screening procedures can be carried out to assess the ability of a compound to act as a **calcilytic** or calcimimetic by measuring its ability to have one or more activities of a **calcilytic** or calcimimetic. In the case of parathyroid cells, such activities include the effects on intracellular calcium, inositol phosphates, cyclic AMP. . .

DETD . . . to its use to inhibit PTH in human cells or test animals. Typically, all the various tests for calcimimetic or **calcilytic** activity are not performed. Rather, if a molecule causes the mobilization of intracellular Ca.sup.2+ in a PMA-sensitive manner, it is. . . for primary or secondary hyperparathyroidism. The lower the EC.sub.50 or IC.sub.50, the more potent the molecule as a calcimimetic or **calcilytic**.

DETD Calcimimetic and **calcilytic** molecules affecting PTH secretion are then preferably assessed for selectivity, for example, by also examining the effects of such compounds. . .

DETD The following is illustrative of methods useful in these screening procedures. Examples of typical results for various test calcimimetic or **calcilytic** molecules are provided in FIGS. 2-34.

DETD . . . lead molecule to mimic or antagonize the effect of extracellular Ca.sup.2+ , the importance of different functional groups for calcimimetics and **calcilytics** were identified. Of the molecules tested, some are suitable as drug candidates while others are not necessarily suitable as drug. . .

DETD FIG. 36 provides additional examples of molecules expected to act as either **calcilytics** or calcimimetics based upon their structure. In general these molecules were synthesized based on the lead molecule, fendiline, and tested. . .

DETD The examples described herein demonstrate the general design of molecules useful as ionomimetics and ionolytics, preferably, calcimimetics and **calcilytics**. The examples also describe screening procedures to obtain additional molecules, such as the screening of natural product libraries. Using these procedures, those of ordinary skill in the art can identify other useful ionomimetics and ionolytics, preferably calcimimetics and **calcilytics**.

DETD . . . carbon atom or a nitrogen atom, preferably at a nitrogen atom. A nitrogen atom branch point is typically a tertiary **amine**, but it may also be quaternary. A branched polyamine may have 1 to 20 branch points, preferably 1 to 10. . .

DETD . . . is an aryl group, preferably a carbocyclic aryl group such as phenyl or a bicyclic carbocyclic aryl groups such as **naphthyl**, preferably 1-**naphthyl**. Especially preferred are R-isomers.

DETD . . . ##STR6## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp.sup.2 or preferably sp.sup.3 hybridization) Ar=(preferably) phenyl, 1-, or 2-**naphthyl**

DETD . . . ##STR7## Alkyl=C.sub.1 -C.sub.6 cyclic, preferably linear, or more preferably branched hydrocarbon (sp.sup.2 or preferably sp.sup.3 hybridization). Ar.sup.1 =(preferably) phenyl or 2-naphthyl; Ar.sup.2 (preferably)=phenyl or 1-naphthyl. R.sup.1 =(preferably) methyl, R.sup.2 =(preferably) H

DETD Ar=any aromatic, heteroaromatic, or heterocyclic system, preferably phenyl, 1-naphthyl, 2-naphthyl, biphenyl, tetrahydronaphthyl, indanyl, indenyl, fluorenyl, 9,10-dihydranthracenyl, 9,10-dihydrophenanthrenyl, pyrrolyl, furanyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, thiofuranyl, isoxazolyl, pyridinyl, pyridazinyl, . . .

DETD . . . are used to provide additional functionality to the molecules, apart from the molecules' ability to act as a calcimimetic or **calcilytic**. These additional components include targeting components and functionalities such as labels which enhance a molecule's ability to be used in. . .

DETD . . . described by Bradford C VanWagenen, Steven R Duff, William A. Nelson and Thomas E. D'Ambra in U.S. patent application, entitled "**Amine** Preparation" hereby incorporated by reference herein.

DETD . . . polyamines such as spermidine or spermine. Strategies for the synthesis and the modification of polyamines involve using a variety of **amine**-protecting groups (e.g., phthalimido, BOC, CBZ, benzyl, and nitrile) which can be selectively removed to construct functionalized molecules.

DETD . . . of the starting material, by 2-4 methylenes were typically accomplished by alkylation with the corresponding N-(bromoalkyl)phthalimide. A 1:1.2 mixture of **amine** to the bromoalkylphthalimide was refluxed in acetonitrile in the presence of 50% KF on Celite. Chain extensions were also accomplished by alkylation of a given **amine** with acrylonitrile or ethylacrylate. Reaction progress was monitored by thin-layer chromatography (TLC) and intermediates purified on-silica gel using combinations of. . .

DETD **Amine**-protecting groups, phthalimido, BOC, CBZ, benzyl, and nitrile, were added and later selectively removed to construct functionalized molecules. BOC protecting groups were added by treating a primary or secondary **amine** (1.degree. or 2.degree.) with di-tert-butyl dicarbonate in dichloromethane. Benzyl protecting groups were applied in one of two ways: (1) condensation of a 1.degree. **amine** with benzaldehyde followed by sodium borohydride reduction or (2) alkylation of a 2.degree. **amine** with benzylbromide in the presence of KF.

DETD Amide linkages were typically prepared by reacting an **amine** (1.degree. or 2.degree.) with an N-hydroxysuccinimide or p-nitrophenylester of a given acid. This was accomplished directly, in the case of adding cyclic groups, by treating the **amine** with dicyclohexylcarbodiimide under dilute conditions.

DETD . . . or "masked" with a protecting group such as BOC (t-butyloxycarbonyl), phthalimido, benzyl, 2-ethylnitrile (the Michael condensation production product of an **amine** and acrylonitrile), or amide. A typical reaction is the addition of a BOC protecting group by treatment with di-t-butyl-dicarbonate (BOC. . .

DETD The remaining free **amine** in the monoprotected product is then selectively alkylated (or acylated) with an alkylating (or acylating) agent. To ensure mono-alkylation, the free **amine** is partially protected by condensation with benzaldehyde followed by sodium borohydride reduction to form the N-benzyl derivative: ##STR10## The N-benzyl. . .

DETD The protecting groups of the resulting chain-extended molecule can then be selectively cleaved to yield a new free **amine**. For example, trifluoroacetic acid is used to remove a BOC group; catalytic hydrogenation is used to reduce a nitrile functionality. . .

DETD The new free **amine** may be alkylated (or acylated) further as

above to increase the length of the polyamine. This process is repeated until. . .

DETD . . . R" depict appropriately substituted hydrocarbon and aromatic moieties groups. Referring to FIG. 43a in a 4-ml vial, 1 mmole of **amine** (1) (typically a primary **amine**) and 1 mmole ketone or aldehyde (2) (generally an appropriately substituted acetophenone) are mixed, then treated with 1.25 mmoles titanium(IV) isopropoxide (3) and allowed to stand with occasional stirring at room temperature for about 30 minutes. Alternatively, a secondary **amine** may be used in place of (1). Reactions giving heavy precipitates or solids can be heated to their melting point. . .

DETD . . . the addition of about 500 .mu.l water. The reaction mixture is then diluted to about 4 ml total volume with **ethyl** ether and then centrifuged. The upper organic phase is removed and reduced on a rotavapor. The resulting product (6) is. . .

DETD . . . the mechanism(s) as a site of action for the therapeutics described herein effective in the treatment of for example, HPT, **osteoporosis**, and hypertension, and novel therapies for other bone and mineral-related diseases.

DETD . . . Ca.sup.2+ from intracellular stores; and using fluorescent Ca.sup.2+ indicators. Expression assays can also be used to measure the calcimimetic and **calcilytic** activity of agents using Xenopus egg containing nucleic acid expressing a functioning calcium receptor.

DETD . . . plasma levels of calcitonin is associated with an inhibition of bone resorption. Inhibiting bone resorption is an effective treatment for **osteoporosis**. Thus, modulation of calcium receptor activity can be used to treat diseases such as hyperparathyroidism, and **osteoporosis**.

DETD . . . activity, can be used to confer beneficial effects to patients suffering from a variety of diseases or disorders. For example, **osteoporosis** is an age-related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds can be used. . . either directly (e.g., an osteoclast ionomimetic compound) or indirectly by increasing endogenous calcitonin levels (e.g., a C-cell calcimimetic). Alternatively, a **calcilytic** active on the parathyroid cell calcium receptor will increase circulating levels of parathyroid hormone, stimulating bone formation. All three of these approaches will result in beneficial effects to patients suffering from **osteoporosis**.

DETD . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionolytic) can increase bone mass in patients suffering from **osteoporosis**.

DETD Ionomimetics and ionolytics, such as calcimimetics and **calcilytics** can be used to assay the responsiveness of a cell or tissue to extracellular calcium. For example, a tissue or. . .

DETD . . . The cloned receptor can be inserted into a cell, such as an oocyte, and its responsiveness to a calcimimetic or **calcilytic** determined. Another example of using hybridization assay probes to detect defects involves using the probes to detect mRNA levels or. . .

DETD Screening for Calcimimetic and **Calcilytic** Activity on the Osteoclast Calcium Receptor

DETD . . . inhibiting bone resorption. Drugs that target the calcium receptors on both of these cells might be very effective therapies for **osteoporosis**. Because PTH is also involved in regulating bone metabolism, drugs acting on the parathyroid cell calcium receptor may also be useful in the treatment and/or prevention of **osteoporosis**.

DETD . . . which then acts on osteoclasts to inhibit bone resorption. Calcimimetic drugs selectively affecting C-cells are useful in the treatment of **osteoporosis**.

DETD **Calcilytic** Activity of NPS 021 on Parathyroid Cells

DETD For a compound to be considered a **calcilytic**, it must block

the effects of extracellular Ca^{2+} or a calcimimetic compound on an extracellular Ca^{2+} -sensing cell. An example of a **calcilytic** compound is NPS 021, the structure of which is provided in FIG. 1a. In bovine parathyroid cells loaded with fura-2, . . . itself cause any change in $[\text{Ca}^{2+}]_{\text{sub.i}}$ when tested at low $[\text{Ca}^{2+}]$ (0.5 mM; FIG. 37). Ga^{3+} is also **calcilytic** to *Xenopus* oocytes expressing the cloned calcium receptor: Ga^{3+} by itself has no effect on the Cl^- currents activated by. . .

DETD In another example, a compound acting as an antagonist (**calcilytic**) at the C-cell calcium receptor can be administered as described above to diagnose medullary thyroid carcinoma. In this case, administration of the C-cell calcium receptor **calcilytic** compound will depress serum levels of calcitonin which can be readily measured by radioimmunoassay. Certain symptoms associated with medullary thyroid. . . carcinoma, such as diarrhea, may also be monitored to determine if they are abated or lessened following administration of the **calcilytic** compound.

DETD . . . specific calcimimetic on the osteoclast calcium receptor can be used in the differential diagnosis of high- and low-turnover forms of **osteoporosis**. In this case, such a compound can be administered in a suitable pharmaceutical preparation and the levels of serum alkaline. . . well known in the art. A large decrease in one or more of these parameters would be predictive of high-turnover **osteoporosis**, whereas a small or no decrease in these parameters would be predictive of low-turnover **osteoporosis**. Such information would dictate the appropriate treatment. Antiresorptive drugs would not be the appropriate sole therapy for low-turnover **osteoporosis**.

DETD . . . the observed effects of such preparations on bodily functions and/or chemical constituents can be used diagnostically. In general, calcimimetic and **calcilytic** compounds that act on calcium receptors of the various cells described above can be used in the diagnosis of the. . .

DETD (4) Calcimimetics are expected to increase platelet aggregability, which may be useful when platelet counts are low. Conversely, **calcilytics** are expected to inhibit platelet function in states where there is hypercoagulability.

DETD . . . the therapy of hypercalcemia and its symptoms. A calcimimetic may also improve hypocalcemic symptoms by activating calcium receptors. Conversely, a **calcilytic** is expected to reduce urinary calcium excretion and be useful in the treatment of kidney stones. In addition, Calcium suppresses. . .

DETD (7) Endogenous amines could reproduce the symptoms in uremic patients by calcimimetic or **calcilytic** actions. Calcimimetic and/or **calcilytic** agents are expected to improve these symptoms.

DETD (9) Some of the genetic component of calcium-related disorders, such as **osteoporosis**, renal stones, and hypertension are expected to be related to inherited problems with certain forms of the receptor. These now. . .

DETD . . . increase in mRNA transcripts would be expected to increase PTH synthesis, resulting in a larger reserve of PTH for secretion. **Calcilytic** compounds might therefore cause an augmented release of PTH when administered after a drug that blocks influx of extracellular Ca^{2+} . . .

DETD . . . and 17P, are provided below. Compounds 4L, 8J, 8U, 11X and 17M were prepared from the condensation of a primary **amine** with an aldehyde or ketone in the presence of titanium(IV) isopropoxide. The resulting intermediate imines were then reduced in situ. . .

DETD Compounds 9R, 14U, and 17P were synthesized by reductive amination of a commercially available aldehyde or ketone with a primary **amine** in the presence of sodium cyanoborohydride or sodium triacetoxyborohydride. It was found for the syntheses of these three

compounds (9R, . . .

DETD Compounds 12U, 12V and 12Z were prepared by a diisobutylaluminum hydride (DIBAL-H)-mediated condensation of an **amine** with a nitrile. The resulting intermediate imine is reduced in situ by the action of sodium cyanoborohydride or sodium borohydride.. . .

DETD N-3-Phenyl-1-propyl-1-(1-**naphthyl**)ethylamine

DETD (R,R)-N-(1-(2-**Naphthyl**)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**) ethylamine (10.0 g, 58 mmol), 2'-acetonaphthone (9.4 g, 56 mmol), titanium (IV) isopropoxide (20.7 g, 73.0 mmol), and EtOH (abs.).. . .

DETD (R)-N-(4-Isopropylbenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**) ethylamine (1.06 g, 6.2 mmol), 4-isopropylbenzaldehyde (0.92 g, 6.2 mmol), and titanium (IV) isopropoxide (2.2 g, 7.7 mmol) was heated. . . .

DETD (R)-N-3-(2-Chlorophenyl)-1-propyl-1-(1-**naphthyl**)ethylamine hydrochloride

DETD The compound was prepared following the procedures described in Example 48, but using 2-chlorohydrocinnamonitrile and (R)-(+)-1-(1-**naphthyl**)ethylamine on a 10-mmol scale. Chromatography through silica gel using a gradient of dichloromethane to 5% methanol in dichloromethane afforded the. . . .

DETD (R,R)-N-(1-(4-Methoxyphenyl)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (1.1 g, 6.2 mmol), 4'-methoxyacetophenone (0.93 g, 6.2 mmol), titanium (IV) isopropoxide (2.2 g, 7.7 mmol), and EtOH (abs.) (1. . . . chromatographed [Selectosil, 5-.mu.M silica gel; 25 cm.times.10.0 mm (Phenomenex, Torrance, Calif.), 4 mL per minute; UV det. 275 nm; 12% **ethyl** acetate-88% hexane (elution time, 12.0 min)]. The HPLC purified diastereomer was then dissolved in hexane and ethereal HCl was added. . . .

DETD (R)-N-(3-Chloro-4-methoxybenzyl)-1-(1-**naphthyl**)ethylamine hydrochloride

DETD A mixture of (R)-(+)-1-(1-**naphthyl**)ethylamine (6.6 g, 39 mmol), 3'-chloro-4'-methoxybenzaldehyde (6.6 g, 39 mmol), titanium (IV) isopropoxide (13.8 g, 48.8 mmol), and EtOH (abs.) (30. . . .

DETD (R,R)-N-(1-(4-Methoxy-3-methylphenyl)ethyl)-1-(1-**naphthyl**)ethylamine hydrochloride [Compound 17P]

DETD A mixture of (R)-(+)-1-(1-**naphthyl**) ethylamine (4.24 g, 24.8 mmol), 4'-methoxy-3'-methylacetophenone (4.06 g, 24.8 mmol), titanium (IV) isopropoxide (8.8 g, 30.9 mmol), and EtOH (abs.).. . .

DETD (R,R)-N-(1-**Ethyl**-4'-methoxy-3'-chlorophenyl)-1-(1-naphthylethyl)**amine**

DETD A mixture of 3'-chloro-4'-methoxyacetophenone (5.3 g, 29 mmol), (R)-(+)-1-(1-**naphthyl**) ethylamine (4.98 g, 29 mmol), titanium (IV) isopropoxide (10.2 g, 36 mmol), and isopropanol (20 mL) was heated to 100.degree.. . .

CLM What is claimed is:

20. A purified nucleic acid comprising a nucleic acid sequence encoding an **amine** acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO:6, SEQ ID NO:7 and SEQ. . . .

21. The nucleic acid of claim 20, wherein said **amine** acid sequence is SEQ ID NO: 5.

22. The nucleic acid of claim 20, wherein said **amine** acid sequence is SEQ ID NO: 6.

23. The nucleic acid of claim 20, wherein said **amine** acid sequence is SEQ ID NO: 7.

=> d his

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L1 157 S OSTEOPOROSIS AND CALCILYT?
L2 26 S L1 AND NAPHTHYL AND ETHYL AND AMINE

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L1 157 OSTEOPOROSIS AND CALCILYT?

=> s l1 and naphthyl and ethyl and amine
L2 26 L1 AND NAPHTHYL AND ETHYL AND AMINE

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L2 ANSWER 1 OF 26 IFIPAT COPYRIGHT 2003 IFI on STN
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TI METHOD OF USING **CALCILYTIC** COMPOUNDS; ALPHA,
ALPHA-DISUBSTITUTED ARYLALKYLAMINE DERIVATIVES
INF Barmore; Robert M., Salt Lake City, UT
Callahan; James F., Philadelphia, PA
Del Mar; Eric G., Salt Lake City, UT
Keenan; Richard M., Malvern, PA
Kotecha; Nikesh R., Thurmaston, GB
Lago; Maria Amparo, Audobon, PA
Sheehan; Derek, Salt Lake City, UT
Southall; Linda Sue, West Chester, PA
Thompson; Mervyn, Harlow Essex, GB
Van Wagenen; Bradford C., Salt Lake City, UT
IN Barmore Robert M; Callahan James F; Del Mar Eric G; Keenan Richard M;
Kotecha Nikesh R (GB); Lago Maria Amparo; Sheehan Derek; Southall Linda
Sue; Thompson Mervyn (GB); Van Wagenen Bradford C
PAF NPS Pharmaceuticals, Inc., Salt Lake City, UT
SmithKline Beecham, Corp., Philadelphia, PA
SmithKline Beecham, PLC, Brentford, GB
PA NPS Pharmaceuticals Inc
Smithkline Beecham Corp
SmithKline Beecham PLC GB
(23499, 28684, 36782)
EXNAM Raymond, Richard L
AG Lyon & Lyon LLP
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AI US 1997-832984 19970404
XPD 9 Apr 2016
RLI US 1996-629608 19960409 CONTINUATION-IN-PART ABANDONED
US 1996-32263 19961203 CONTINUATION-IN-PART
PRAI US 1996-32263P 19961203 (Provisional)
FI US 6022894 20000208
DT UTILITY; CERTIFICATE OF CORRECTION
CDAT 29 Jan 2002
FS CHEMICAL
GRANTED
OS CA 132:151556
MRN 008970 MFN: 0633
008970 0654
CLMN 30
AB The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
receptor activity. Also described are the use of **calcilytic**
compounds to inhibit calcium receptor activity and/or achieve a
beneficial effect in a patient; and techniques which can be used to
obtain additional **calcilytic** compounds.
TI METHOD OF USING **CALCILYTIC** COMPOUNDS; ALPHA,
ALPHA-DISUBSTITUTED ARYLALKYLAMINE DERIVATIVES
AB The present invention features **calcilytic** compounds. "
Calcilytic compounds" refer to compounds able to inhibit calcium
receptor activity. Also described are the use of **calcilytic**
compounds to inhibit calcium receptor activity and/or achieve a
beneficial effect in a patient; and techniques which can be used to
obtain additional **calcilytic** compounds.
ECLM . . . A method of treating a patient comprising the step of
administering to said patient a therapeutically effective amount of a
calcilytic compound having the formula:

R1-Z-Y1-C(-R2)(-R6)-Y2-NH-C(-R3)(-R4)-Y3-R5

wherein R1 is selected from the group consisting of: aryl,
longer-length. . .
ACLM . . . selected from the group consisting of: osteosarcoma, periodontal
disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's
disease, humoral hypercalcemia malignancy, and **osteoporosis**.
4. The method of claim 3, wherein disease or disorder is
osteoporosis.
5. A method of treating a patient comprising the step of administering to
said patient an amount of a **calcilytic** compound sufficient to
increase serum PTH level, said compound having the formula:

D R A W I N . . .

. . . The method of any one of claims 1-12, wherein R5 is either an
optionally substituted phenyl or an optionally substituted
naphthyl.
17. The method of claim 16, wherein Z is O or methylene, R2 is OH, R3 is
methyl or **ethyl**; and R4 is methyl or **ethyl**.
24. The method of claim 17, wherein R5 is a substituted **naphthyl**
having one to four substituents each independently selected from the
group consisting of: alkoxy, lower-haloalkyl, S-lower alkyl,
lower-haloalkoxy, lower alkyl, . . .
26. The method of claim 17, wherein R5 is **naphthyl**.
30. The method of claim 14, wherein said compound is selected from the
group consisting of: (R)-N-(2-hydroxy-3-(3-chloro-2-cyanophenoxy)propyl)-
1,1-dimethyl-2-(4-methoxyphenyl)ethylamine; (R)-N-(2-hydroxy-3-((2,3-
dichloro-4-dipropylsulfamoyl)phenoxy)-1-propyl)-N-(1,1-dimethyl-2-(4-
methoxyphenyl)**ethyl**)amine; N-(2-hydroxy-3-
phenoxypropyl)-1,1-dimethyl-2-(2-**naphthyl**) ethylamine;
(R)-N-(2-hydroxy-3-(2,3-dichlorophenoxy)propyl)-1,1-dimethyl-2-(4-
methoxyphenyl)ethylamine; (R)-N-(2-hydroxy-3-(2-cyanophenoxy)propyl)-1,1-
dimethyl-2-(4-methoxyphenyl)-ethylamine; and N-(2-hydroxy-3-(2-
nitrophenoxy)propyl)-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine; or a
pharmaceutically acceptable salt or complex thereof.

L2 ANSWER 2 OF 26 USPTAFULL on STN
AN 2003:300884 USPTAFULL
TI **Calcilytic** compounds
IN Bhatnagar, Pradip K., King of Prussia, PA, UNITED STATES
Callahan, James F., Collegeville, PA, UNITED STATES
Lago, Amparo M., Collegeville, PA, UNITED STATES
PI US 2003212110 A1 20031113
AI US 2003-333096 A1 20030115 (10)
WO 2001-US22267 20010716
DT Utility
FS APPLICATION
LREP SMITHKLINE BEECHAM CORPORATION, CORPORATE INTELLECTUAL PROPERTY-US,
UW2220, P. O. BOX 1539, KING OF PRUSSIA, PA, 19406-0939
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 952
AB Novel **calcilytic** compounds and methods of using them are
provided.
TI **Calcilytic** compounds
AB Novel **calcilytic** compounds and methods of using them are
provided.
SUMM [0001] The present invention relates to novel **calcilytic**
compounds, pharmaceutical compositions containing these compounds and
their use as calcium receptor antagonists.
SUMM [0006] Various compounds are known to mimic the effects of
extra-cellular Ca.sup.2+ on a calcium receptor molecule.

Calcilytics are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM [0022] Ar is phenyl or **naphthyl**, unsubstituted or substituted, heteroaryl or fused heteroaryl, such that the hetero-ring may contain N, O or S and may be. . .

SUMM . . . systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and **naphthyl**. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halogen, C.sub.1-4 alkyl OCF.sub.3, CF.sub.3, OMe, . . .

SUMM . . . reaction continued overnight to give the corresponding glycidyl ether (Scheme 1). A solution of the substituted glycidyl ether and excess **amine** (e.g., 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine) in absolute ethanol, acetonitrile, THF, dioxane or any other similar solvent in the presence of a suitable catalyst. . .

SUMM [0058] The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM [0062] The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50, . . .

SUMM . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.

SUMM [0083] **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

SUMM [0092] 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

SUMM [0096] A typical reaction mixture contains 2 nM .sup.3H compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-**naphthyl**)ethylamine), or .sup.3H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume. . .

DETD [0100] a) 5-(4-Cyano-3-fluoro-phenyl)-nicotinic acid **ethyl** ester

DETD . . . residue is treated with 4N HCl/dioxane in refluxing ethanol for 18 h. The reaction is evaporated and the residue in **ethyl** acetate is washed with NaHCO.sub.3 (aqueous), dried over MgSO.sub.4 and evaporated to give 5-(4-cyano-3-fluoro-phenyl)-nicotinic acid **ethyl** ester.

DETD [0102] b) 5-(4-Cyano-3-hydroxy-phenyl)-nicotinic acid **ethyl** ester

DETD [0103] A mixture of 5-(4-cyano-3-fluoro-phenyl)-nicotinic acid **ethyl** ester from Example 1a, potassium acetate (2 equiv.), and 18-crown-6 ether (2 equiv.) in MeCN is heated at reflux in. . . neutralized with 1N HCl, extracted with EtOAc, dried over MgSO.sub.4, and concentrated. Purification by flash column chromatography gives 5-(4-cyano-3-hydroxy-phenyl)-nicotinic acid **ethyl** ester.

DETD [0104] c) 5-(4-Cyano-3-R-oxiranylmethoxy-phenyl)-nicotinic acid **ethyl** ester

DETD [0105] A mixture of the 5-(4-cyano-3-hydroxy-phenyl)-nicotinic acid **ethyl** ester from Example 1b (1 equiv.), potassium carbonate (2 equiv.), and R-glycidyl-3-nitrobenzenesulfonate (1 equiv.) in acetone is heated at reflux in 24 h. The mixture is cooled, concentrated, taken up in H.sub.2O and is extracted with **ethyl** acetate. The organic extracts are washed with brine, dried over MgSO.sub.4, concentrated to afford 5-(4-cyano-3-R-oxiranylmethoxy-phenyl)-nicotinic acid **ethyl** ester.

DETD [0107] A mixture of 5-(4-cyano-3-R-oxiranylmethoxy-phenyl)-nicotinic acid **ethyl** ester from Example 1c (1 equiv.), lithium perchlorate (1 equiv.), and 1,1-dimethyl-2-(5-chlorothienyl)ethylamine (1.1 equiv.) in dioxane is heated at reflux. . .

DETD [0119] a) 6-(4-Cyano-3-R-oxiranylmethoxy-phenyl)-pyridine-2-carboxylic acid **ethyl** ester.

DETD . . . Utilizing the procedure outlined in Example 1a-c but replacing 4-bromonicotinic acid with 6-bromopicolinic acid in Example 1a give 6-(4-Cyano-3-R-oxiranylmethoxy-phenyl)-pyridine-2-carboxylic acid **ethyl** ester.

DETD . . . iodide (1 equiv.) is added and stirred for 18 h. The reaction mixture is evaporated, the residue is taken into **ethyl** acetate, washed with 5% Na.sub.2CO.sub.3 (aqueous), dried over MgSO.sub.4 and evaporated to give 2-bromo-3-methoxy-pyridine.

DETD . . . is treated with NaCN at 120.degree. C. for 18 h. The reaction mixture is evaporated, the residue is taken into **ethyl** acetate, washed with 5% Na.sub.2CO.sub.3 (aqueous), dried over MgSO.sub.4 and evaporated to give 3-methoxy-pyridine-2-carbonitrile.

DETD . . . catalytic 2,2-azobisisobutyronitrile and is heated at reflux for 18 h. The reaction mixture is evaporated, the residue is taken into **ethyl** acetate, washed with 5% Na.sub.2CO.sub.3 (aqueous), 5 % Na.sub.2S.sub.2O.sub.3 (aqueous), dried over MgSO.sub.4 and evaporated to give 6-bromo-3-methoxy-pyridine-2-carbonitrile.

DETD [0140] d) 4-(6-Cyano-5-methoxy-pyridin-2-yl)-benzoic acid **ethyl** ester

DETD . . . N HCl in dioxane and heated at reflux for 18 h. The reaction mixture is evaporated, the residue taken into **ethyl** acetate, washed with 5% Na.sub.2CO.sub.3 (aqueous), dried over MgSO.sub.4 and evaporated to give 4-(6-cyano-5-methoxy-pyridin-2-yl)-benzoic acid **ethyl** ester.

DETD [0142] e) 4-(6-Cyano-5-hydroxy-pyridin-2-yl)-benzoic acid **ethyl** ester

DETD [0143] A solution of 4-(6-cyano-5-methoxy-pyridin-2-yl)-benzoic acid **ethyl** ester from Example 13d in collidine is treated with LiI and heated at 120.degree. C. for 24 h. The reaction. . . taken into water and neutralized with 1 N HCl. The resulting precipitate is collected and dried to give 4-(6-cyano-5-hydroxy-pyridin-2-yl)-benzoic acid **ethyl** ester.

DETD [0144] f) 4-(6-Cyano-5-oxiranylmethoxy-pyridin-2-yl)-benzoic acid

ethyl ester

DETD . . . heated at reflux in 24 h. The mixture was cooled, concentrated, is taken up in H.sub.2O and is extracted with **ethyl** acetate. The organic extracts are washed with brine, dried over MgSO.sub.4, and concentrated to afford 4-(6-cyano-5-oxiranylmethoxy-pyridin-2-yl)-benzoic acid **ethyl ester**.

CLM What is claimed is:

- . . . alkyl, or R.sub.1', and R.sub.1" together form a 3 to 7 membered optionally substituted heterocyclic ring; Ar is phenyl or **naphthyl**, unsubstituted or substituted, heteroaryl or fused heteroaryl, such that the hetero-ring may contain N, O or S and may be.
- . . . the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, joint replacement, rheumatoid arthritis, Paget's disease, humoral hypercalcemia, malignancy and **osteoporosis**.

6. A method according to claim 5 wherein the bone or mineral disease or disorder is **osteoporosis**.

L2 ANSWER 3 OF 26 USPATFULL on STN

AN 2003:251696 USPATFULL

TI Calcium receptor active compounds

IN Sakai, Teruyuki, Gunma, JAPAN

Takami, Atsuya, Gunma, JAPAN

Nagao, Rika, Gunma, JAPAN

PA NPS Pharmaceuticals, Inc. (non-U.S. corporation)

PI US 2003176485 A1 20030918

AI US 2002-243322 A1 20021121 (10)

RLI Continuation of Ser. No. US 2002-53133, filed on 17 Jan 2002, PENDING

DT Utility

FS APPLICATION

LREP NPS PHARMACEUTICALS, INC. C/O FOLEY & LARDNER, P.O. BOX 80278, SAN DIEGO, CA, 92138-0278

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 94 Drawing Page(s)

LN.CNT 10464

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl, bis(arylmethyl)amino, bis(heteroarylmethyl)amino and arylmethyl(heteroarylmethyl) amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl, sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8 and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

SUMM . . . one or more of the rings has a completely conjugated pi-electron system. Examples, without limitation, of aryl groups, are phenyl, **naphthyl**, anthracenyl, phenanthrenyl, fluorenyl, and indanyl. The aryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably. . .

SUMM . . . or more halogens and, combined, unsubstituted cycloalkyl and cycloalkenyl. Also preferably, Art is selected from the group consisting of phenyl, **naphthyl**, indolyl, fluorenyl, dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl, pyridin-4-yl, quinolin-2-yl and dibenzylamino and Ar.sub.2 is selected from the group consisting of phenyl, **naphthyl**, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl. More preferably, Ar.sub.1 is phenyl substituted with one. . . alkoxy, trihalomethoxy, trihaloacetyl and nitro, and Ar.sub.2 is selected from the group consisting of optionally substituted phenyl and optionally substituted **naphthyl**. Even more preferably, Ar.sub.2 is 3-methoxyphenyl or unsubstituted **naphthyl**. Preferably, R.sup.8 is hydrogen, R.sup.9 is methyl and X is oxygen or sulfur.

SUMM . . . halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted **naphthyl**; and Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from. . . one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted **naphthyl**.

SUMM . . . substituted with one or more halogens and lower alkoxy substituted with one or more halogens; and Ar.sub.6 is 3-methoxyphenyl or .alpha.-**naphthyl**, more preferably, .alpha.-**naphthyl**. Also preferably, Ar.sub.5 is dibenzylamino, benzyl(naphthylmethyl) amino or benzyl(pyridylmethyl) amino optionally substituted with one or more groups independently selected from. . . lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens, and Ar.sub.6 is **naphthyl** or methoxyphenyl. More preferably, Ar.sub.5 is dibenzylamino optionally substituted with unsubstituted alkyl, and Ar.sub.6 is .alpha.-**naphthyl**.

SUMM . . . the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (calcimimetic modulation) or blocking the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (**calcilytic** modulation); preferably calcimimetic modulation.

SUMM . . . aspect, the present invention provides a method for the treatment or prevention of primary and secondary hyperparathyroidism, renalosteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering a therapeutically effective amount of a compound of this invention to a patient.

SUMM . . . affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, **osteoporosis** is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic. . . levels (e.g., a parathyroid cell ionmimetic) can retard bone loss and, thus, result in beneficial effects to patients suffering from **osteoporosis**.

SUMM . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from **osteoporosis**.

SUMM . . . modulates one or more effects of an inorganic ion receptor: Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and **calcilytics**.

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. **Calcilytics** are ionlytics which inhibit one or

more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium. . .

SUMM . . . preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis**, renalosteodystrophy and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as.

. .

SUMM . . . Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism, renalosteodystrophy and **osteoporosis**.

DETD . . . mimic or block an effect of extracellular $\text{Ca}_{\text{sup.2+}}$ on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and **calcilytics**.

DETD [0235] Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC_{50} or IC_{50} at a calcium receptor of less than or equal to 5 mM, and even more. . .

DETD [0237] In another preferred embodiment the calcium receptor modulating agent is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . .

DETD . . . need not possess all the biological activities of extracellular $\text{Ca}_{\text{sup.2+}}$, but, rather, at least one such activity is mimicked. Similarly, **calcilytics** need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular $\text{Ca}_{\text{sup.2+}}$ to exert their. . .

DETD [0257] B. **Calcilytics**

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

. .

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of

sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was added to the reaction mixture. Then the mixture was stirred at room temperature, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 17.31 g (87.8%) of colorless prism crystals 48.

DETD . . . 6 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 36.8 g (82.8%) of colorless prism crystals 49.

DETD . . . C. for 2.5 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 52.

DETD . . . (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 162.7 mg (0.95 mmol, 2.0 moleq.) of (R)-1-(1-naphthyl)ethylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an. . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated

aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 53.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 723.4 mg (87.0%) of a colorless oil 55.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 56.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 202.4 mg (73.3%) of a colorless prism crystals 58.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 59.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 824.0 mg (84.9%) of a colorless oil 61.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 222.6 mg (87.1%) of a colorless oil 62.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the

obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 884.2 mg (91.1%) of a colorless oil 64.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 229.3 mg (89.7%) of a colorless oil 65.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 876.5 mg (90.3%) of a colorless oil 67.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 293.1 mg (87.2%) of a colorless oil 68.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 804.3 mg (77.0%) of colorless prism crystals 70.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 880.8 mg (89.5%) of a colorless oil 71.

DETD . . . temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 551.8 mg (100%) of a colorless oil 73.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 230.8 mg (91.3%) of a colorless oil 74.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous

solution of hydrochloric acid, water and a saturated aqueous solution of sodium. . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 241.3 mg (45.9%) of a colorless oil 76.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 209.8 mg (69.7%) of a colorless oil 77.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 586 mg (61.4%) of a colorless oil 79.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 265.1 mg (82.8%) of a colorless oil 80.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 564.9 mg (82.5%) of colorless prism crystals 82.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 311.9 mg (83.8%) of colorless prism crystals 83.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 85.

DETD . . . acidified with a 5% aqueous solution of hydrochloric acid. Then the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium. . . sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 86.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure,

the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 615.4 mg (98.5%) of colorless prism crystals 87.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with ethyl acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 76.3 mg (82.6%) of a colorless oil 88.

DETD [0393] To a solution of 600 mg (3.5 mmol) of (R)-1-(1-naphthyl)ethylamine 89 in 5 ml of methylene chloride were added 580.3 mg (d=1.176, 3.85 mmol, 1.1 moleq.) of ethylmalonyl chloride and . . . and dried over sodium sulfate. After distilling off the solvent, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 662.9 mg (66.5%) of colorless prism crystals 90.

DETD . . . concentrated, acidified with a 5% aqueous solution of hydrochloric acid. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 596.0 mg (99.8%) of colorless prism crystals 91.

DETD . . . (1.56 mmol) of the compound 91 in 5 ml of dimethylformamide were added 293.2 mg (1.71 mmol, 1.1 moleq.) of (R)-1-(1-naphthyl)ethylamine and 359.2 mg (1.87 mmol, 1.2 moleq.) of WSC.times.HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 615.1 mg (96.4%) of colorless prism crystals 92.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with ethyl acetate. The hydrochloric acid layer was made alkaline by adding a 5%-aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 82.0 mg (88.0%) of a colorless oil 93.

DETD [0402] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 361.8 mg (80.0%) of the compound 102 as colorless prisms.

DETD . . . a solution of the above compound 102 (125.8 mg, 0.38 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0406] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.1 mg (89.5%) of the compound 103 as a colorless oil.

DETD [0410] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, n-hexane/**ethyl** acetate] to thereby give the compound 105 (723.4 mg, 87.0%) as a colorless oil.

DETD . . . a solution of the above compound 105 (106.2 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (48.4 mg, 0.35 mmol, 1.2 mol eq.) and the resulting mixture was stirred. . .

DETD [0413] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 33.7 mg (76.1%) of the compound 106 as a colorless oil.

DETD [0417] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 804.3 mg (77.0%) of the compound 108 as colorless prisms.

DETD . . . a solution of the above compound 108 (106.9 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0420] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.2 mg (58.3%) of the compound 109 as a colorless oil.

DETD [0424] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 586 mg (61.4%) of the compound 111 as a colorless oil.

DETD . . . a solution of the above compound 111 (65.3 mg, 0.26 mmol, 1.5 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (29.3 mg, 0.17 mmol) and potassium carbonate (35.5 mg, 0.26 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0428] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The

ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 36.5 mg (62.0%) of the compound 112 as a colorless oil.

DETD [0431] To a solution of (R)-(+)-1-(1-naphthyl)ethylamine (600 mg, 3.5 mmol) in dichloromethane (5 ml) were added ethylmalonyl chloride 113 (580.3 mg, 3.85 mmol, 1.1 mol eq.). . .

DETD . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 662.9 mg (66.5%) of the compound 114 as colorless prisms.

DETD . . . the reaction mixture was concentrated, acidified with a 5% aqueous solution of hydrochloric acid, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed successively with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 659.5 mg of the compound 115 as colorless prisms.

DETD [0439] To a solution of the above compound 115 (50 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) were added (R)-(+)-1-(1-naphthyl)ethylamine (45.0 mg, 0.21 mmol, 1.1 mol eq.) and WSC.multidot.HCl (44.9 mg, 0.23 mmol, 1.2 mol eq.) and the resulting mixture. . .

DETD [0440] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 61.6 mg (70.5%) of the compound 116 as colorless prisms.

DETD . . . into the reaction mixture. Then the mixture was acidified with a 5% aqueous solution of hydrochloric acid and extracted with ethyl acetate. The layer of the 5% aqueous solution of hydrochloric acid was made alkaline by adding a 5% aqueous solution of sodium hydroxide and then extracted with ethyl acetate. After washing with water and a saturated aqueous solution of sodium chloride and drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 18.0 mg (88.0%) of the compound 117 as a colorless oil.

DETD . . . After the completion of the reaction, ammonium chloride was added thereto in excess and the reaction mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the crystals thus obtained were purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 16.0 g of the compound 119.

DETD [0451] After cooling by allowing to stand, it was purified by column chromatography and eluted with ethyl acetate/n-hexane to thereby give 700 mg of the compound 120.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 1.5 g of the compound 122.

DETD [0458] The above compound 122 (150 mg, 0.51 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (104.5 mg, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (3 ml) and then allowed to stand at

room. . .

DETD Synthesis of K-2027 (N-[5-[(4-chlorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (241 mg, 1.74 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.31 ml, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . C. for 24 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.70 g, 12.3 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.45 ml, 2.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2052 (N-[5-[(4-fluorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (300 mg, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (247 mg, 1.79 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2076 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[(4-(trifluoromethyl)phenyl)thio]pentyl)amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (200 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.28 ml, 1.73 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2087 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[(3-(trifluoromethyl)phenyl)thio]butyl)amine)

DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2117 ((R)-N-(1-(1'-naphthyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine)

DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (4.0 g, 28.9 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (3.70 ml, 22.9 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD [0554] The compound thus obtained (50 mg, 0.20 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (41.0 mg, 0.24 mmol, 1.2 mol eq.) were dissolved in chloroform-methanol (2 ml) and allowed to stand at room temperature. . .

DETD Synthesis of K-2246 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[(4-(trifluoromethyl)phenyl)thio]butyl)amine)

DETD . . . reaction by TLC, 5 ml of acetonitrile, 693 mg (5.01 mmol) of potassium carbonate and 0.49 ml (2.96 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD . . . reaction by TLC, 8 ml of acetonitrile, 853 mg (6.17 mmol) of potassium carbonate and 0.60 ml (3.63 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD Synthesis of K-2243 (N1,N1-di(4-chlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD [0566] After the completion of the reaction, the solvent was distilled off under reduced pressure. **Ethyl** acetate and water were poured into the residue, and filtered through celite. The residue was washed with **ethyl** acetate and then the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0570] 100 mg (0.31 mmol) of the above-mentioned compound 125 and 64.2 mg (0.38 mmol, 1.2 mol eq.) of (R)-(+)-(1-**naphthyl**)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2257 (N1,N1-di[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. **Ethyl** acetate and water were poured into the residue and filtered through celite. The residue was washed with **ethyl** acetate and then the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0576] 450 mg (1.07 mmol) of the above-mentioned compound 127 and 220.7 mg (1.29 mmol, 1.2 mol eq.) of (R)-(+)-(1-**naphthyl**)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2259 (N1,N1-di[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. **Ethyl** acetate and water were poured into the residue and filtered through celite. The residue was washed with **ethyl** acetate and then the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0582] 800 mg (2.06 mmol) of the above-mentioned compound 129 and 424.0 mg (2.48 mmol, 1.2 mol eq.) of (R)-(+)-(1-**naphthyl**)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2247 (N1-benzyl-N-1-(4-chlorobenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0586] The conjugated ketone compound 202 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0590] The conjugated ketone compound 204 (105.8 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0594] The conjugated ketone compound 206 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD Synthesis of K-2250 (N-1-benzyl-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0598] The conjugated ketone compound 208 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0602] The conjugated ketone compound 210 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0606] The conjugated ketone compound 212 (100 mg, 0.35 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (71.8 mg, 0.42 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0610] The conjugated ketone compound 214 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0614] The conjugated ketone compound 216 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0618] The conjugated ketone compound 218 (800 mg, 1.63 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (33.7 mg, 1.95 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0622] The conjugated ketone compound 220 (1 g, 3.13 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (642.2 mg, 3.75 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2262 (N-1-(2-chlorobenzyl)-N-1-(4-chlorobenzyl)-3-(((1R)-1-(1-**naphthyl**)**ethyl**amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0626] The conjugated ketone compound 222 (500 mg, 1.56 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (321.1 mg, 1.88 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2264 (N-1-(3,4-dichlorobenzyl)-N-1-[(4-trifluoromethyl)benzyl]-3-(((1R)-1-(1-**naphthyl**) **ethyl**amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with

ethyl acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0632] The conjugated ketone compound 224 (800 mg, 2.06 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (387.7 mg, 2.26 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2265 (N1,N1-di(3,4-dichlorobenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:**ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 225 (712.2 mg, 74.3%).

DETD [0638] The conjugated ketone compound 226 (280 mg, 0.72 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (148 mg, 0.864 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2266 (N-1-(4-chlorobenzyl)-N-1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0644] The conjugated ketone compound 228 (800 mg, 2.26 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (425.4 mg, 2.48 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2267 (N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0650] The conjugated ketone compound 230 (600 mg, 1.69 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (347.2 mg, 2.03 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2270 (N1,N1-di(4-methoxybenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0656] The conjugated ketone compound 232 (450 mg, 1.45 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (297 mg, 1.74 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2272 (N-1-(3,4-dichlorobenzyl)-N-1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]-amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel,

hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 233 (777.3 mg, 78.2%).

DETD [0662] The conjugated ketone compound 234 (350 mg, 0.87 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (178 mg, 1.04 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2283 (N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 235 (1.092 g, 98.1%).

DETD [0668] The conjugated ketone compound 236 (400 mg, 1.08 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (222 mg, 1.30 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2289 (N1-(4-chlorobenzyl)-N-1-(4-methoxybenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane ethyl acetate (9:1-4:1)] to thereby give a colorless oil 237 (711.8 mg, 74.8%).

DETD [0674] The conjugated ketone compound 238 (414 mg, 1.31 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (270 mg, 1.57 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2290 (N-1-(4-methoxybenzyl)-N-1-[4-(trifluoromethyl)benzyl]-3-[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0680] The conjugated ketone compound 240 (874.7 mg, 2.50 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (513.9 mg, 3.00 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2291 (N-1-(4-chlorobenzyl)-N-1-(2-naphthylmethyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0686] The conjugated ketone compound 242 (500 mg, 1.49 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (307 mg, 1.79 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2294 (N-1-(3,4-dichlorobenzyl)-N-1-(4-methylbenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino}propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0692] The conjugated ketone compound 244 (1.5587 g, 4.67 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (959.6 mg, 5.60 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at

room temperature for. . .

DETD Synthesis of K-2299 (N1-(4-methylbenzyl)-N-1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0698] The conjugated ketone compound 246 (1.4568 g, 4.36 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (896.8 mg, 5.24 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2300 (N1,N1-di(4-methylbenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 247 (819.4 mg, 88.2%).

DETD [0704] The conjugated ketone compound 248 (400 mg, 1.43 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (295 mg, 1.72 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2309 (N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 249 (827.0 mg, 76.8%).

DETD [0710] The conjugated ketone compound 250 (692.4 mg, 1.98 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (407 mg, 2.37 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2310 (N-1-(4-methylbenzyl)-N-1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography (silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 251 (979.1 mg, 80.4%).

DETD [0716] The conjugated ketone compound 252 (685.1 mg, 1.96 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (403 mg, 2.36 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 253 (944.0 mg, 83.4%).

DETD [0721] The conjugated ketone compound 254 (612.8 mg, 1.68 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (345 mg, 2.01 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD [0727] The conjugated ketone compound 256 (260.2 mg, 0.88 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (180 mg, 1.05 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2280 (N-{5-[(4-methoxyphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (931 mg, 6.75 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.52 ml, 3.22 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2281 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[(2,4,5-trichlorophenyl)thio]butyl]amine)
 DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (545 mg, 3.94 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.41 ml, 3.94 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2282 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[5-[(2,4,5-trichlorophenyl)thio]pentyl]amine)
 DETD . . . temperature for 2.5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.00 g, 7.25 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.69 ml, 4.27 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2287 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[[4-(trifluoromethoxy)phenyl]thio]butyl]amine)
 DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (710 mg, 5.14 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.53 ml, 3.28 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2288 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[5-[[4-(trifluoromethoxy)phenyl]thio]pentyl]amine)
 DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (770 mg, 5.57 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.58 ml, 3.59 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2293 (N-[4-[(4-chlorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (775 mg, 5.61 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.62 ml, 3.84 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2240 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[3-[[4-(trifluoromethyl)phenyl]thio]propyl]amine)
 DETD Synthesis of K-2263 (N-[4-[[4-(4-fluorophenyl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2269 (N-[4-[[3-methoxyphenyl]thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2271 (N-[[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2279 (N-[[5-(3-methoxyphenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2284 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[5-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]pentyl]amine)
 DETD Synthesis of K-2286 (N-[6-[(4-chlorophenyl)thio]hexyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2292 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[7-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]heptyl]amine)
 DETD Synthesis of K-2296 (N-[[5-(2,5-dichlorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2297 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[4-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]butyl]amine)
 DETD Synthesis of K-2298 (N-[4-[[2,5-dichlorophenyl]thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
 DETD Synthesis of K-2301 (N-[(1R)-1-(1-naphthyl)ethyl]-N-[6-[[4-(trifluoromethoxy)phenyl]thio]hexyl]amine)

DETD Synthesis of K-2302 (N-{4-[(2,4-dimethylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2303 (N-{5-[(2,4-dimethylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2304 (N-{4-[(4-methylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD Synthesis of K-2305 (N-{5-[(4-methylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine respectively by 3-trifluoromethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-methylbenzylamine. m/z=355.

DETD . . . synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the (R)-(+)-3-methoxy-.alpha.-benzylmethylamine by (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=419.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=349.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the

[illegible]

1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-methoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-methoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z 398.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=444, 446.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1, 4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=447.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,10-dibromodecane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,12-dibromododecane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2-isopropylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1 bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole and

(R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=408.

- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=422.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptabenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=375.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but

replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=355.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=424.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=438.

DETD . . . potassium carbonate (4.04 g) was added thereto. After 1 hour,

water was added and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crystals thus obtained were washed with chloroform to thereby give N-(2-(2',5'-dichlorophenylthio)ethyl)phthalimide (F-8) (8.28 g). MS m/z: 351 (M.sup.+).

- DETD [1286] N-(2-(2',5'-Dichlorophenylthio)ethyl)phthalimide (F-8) (7.06 g) was added to ethanol (120 ml). After further adding hydrazine monohydrate (6.9 ml), the obtained mixture was. . .
- DETD . . . ice-cooling. Then the mixture was brought to room temperature and stirred for 15 hours. The reaction mixture was concentrated and ethyl acetate and water were added thereto. The insoluble matters were filtered off and the organic layer was washed with a. . . sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol=50:1) to thereby give (.+-.)-N-(1-(3-methoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-12) (146 mg).
- DETD [1289] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethoxyacetophenone to thereby give (.+-.)--N-(1-(3,4-dimethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 385 (M.sup.+).
- DETD [1290] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-methylacetophenone to thereby give (.+-.)-N-(1-(3-methylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-14). MS m/z: 339 (M.sup.+).
- DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-methylacetophenone to thereby give (.+-.)-N-(1-(4-methylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 339 (M.sup.+).
- DETD [1292] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4',5'-trimethoxyacetophenone to thereby give (.+-.)--N-(1-(3,4,5-trimethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-16). MS m/z: 415 (M.sup.+).
- DETD [1293] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxyacetophenone to thereby give (.+-.)-N-(1-(4-hydroxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-17). MS m/z: 341 (M.sup.+).
- DETD [1294] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethyl)acetophenone to thereby give (.+-.)-N-(1-(3-trifluoromethylphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-18). MS m/z 393 (M.sup.+).
- DETD [1295] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxy-3'-methoxyacetophenone to thereby give (.+-.)-N-(1-(4-hydroxy-3-methoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-21). MS m/z 371 (M.sup.+)
- DETD [1296] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-bromoacetophenone to thereby give (.+-.)-N-(1-(4-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-22). MS m/z: 405 (M.sup.+).
- DETD [1297] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-bromoacetophenone to thereby give (.+-.)--N-(1-(3-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-23). MS m/z: 405 (M+).
- DETD [1298] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-bromoacetophenone to thereby give (.+-.)--N-(1-(2-bromophenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-24). MS m/z: 405 (M.sup.+).
- DETD [1299] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dihydroxyacetophenone to thereby give (.+-.)-N-(1-(3,4-dihydroxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-29). MS m/z: 357 (M.sup.+).

DETD [1300] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dichloroacetophenone to thereby give (.+-.)-N-(1-(2,5-chlorophenyl)**ethyl**)-2-(2,5'-dichlorophenylthio)ethylamine (F-30). MS m/z: 395 (M.sup.+).

DETD [1301] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoro-4'-methoxyacetophenone to thereby give (.+-.)-N-(1-(3-fluoro-4-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-31). MS m/z: 373 (M.sup.+).

DETD [1302] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethoxy)acetophenone to thereby give (.+-.)-N-(1-(3-trifluoromethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 409 (M.sup.+).

DETD [1303] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethylacetophenone to thereby give (.+-.)-N-(1-(3,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-48). MS m/z: 353 (M.sup.+).

DETD [1304] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-chloroacetophenone to thereby give (.+-.)-N-(1-(2-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-49). MS m/z: 359 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-chloroacetophenone to thereby give (.+-.)-N-(1-(3-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-50). MS m/z: 359 (M.sup.+).

DETD [1306] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-chloroacetophenone to thereby give (.+-.)-N-(1-(4-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-51). MS m/z: 359 (M.sup.+).

DETD [1307] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoroacetophenone to thereby give (.+-.)-N-(1-(3-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-52). MS m/z: 343 (M.sup.+).

DETD [1308] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-fluoroacetophenone to thereby give (.+-.)-N-(1-(4-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-53). MS m/z: 343 (M.sup.+).

DETD [1309] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dimethylacetophenone to thereby give (.+-.)-N-(1-(2,5-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-54). MS m/z: 353 (M.sup.+).

DETD [1310] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dimethylacetophenone to thereby give (.+-.)-N-(1-(2,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-55). MS m/z: 353 (M.sup.+).

DETD [1311] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dichloroacetophenone to thereby give (.+-.)-N-(1-(2,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-57). MS m/z: 395 (M.sup.+).

DETD [1312] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dichloroacetophenone to thereby give (.+-.)-N-(1-(3,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-58). MS m/z: 395 (M.sup.+).

DETD [1313] 3'-Hydroxyacetophenone (200 mg) was dissolved in acetonitrile (4 ml). After adding **ethyl** iodide (0.2 ml) and potassium carbonate (347 mg), the mixture was stirred at 70.degree. C. for 9 hours. After 9 hours, water and **ethyl** acetate were added to the reaction mixture followed by separation. The organic layer was washed with a saturated aqueous solution. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane: **ethyl** acetate=8:1) to thereby give 204 mg of 3'-ethoxyacetophenone. The procedure employed for the synthesis of F-12

was repeated but replacing the 3'-methoxyacetophenone by 3'-ethoxyacetophenone to thereby give (.-.)-N-(1-(3-ethoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-63). MS m/z: 369 (M.sup.+).

DETD [1314] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-propyl iodide to thereby give 3'-n-propoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-propoxyacetophenone to thereby give (.-.)-N-(1-(3-n-propoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-64). MS m/z: 383 (M.sup.+).

DETD [1315] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-butyl iodide to thereby give 3'-n-butoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-butoxyacetophenone to thereby give (.-.)-N-(1-(3-n-butoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-65). MS m/z: 397 (M.sup.+).

DETD [1316] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-hexyl bromide to thereby give 3'-n-hexyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-hexyloxyacetophenone to thereby give (.-.)-N-(1-(3-n-hexyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2255). MS m/z: 425 (M.sup.+).

DETD [1317] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isopropyl iodide to thereby give 3'-isopropoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isopropoxyacetophenone to thereby give (.-.)-N-(1-(3-isopropoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-67). MS m/z: 383 (M.sup.+).

DETD [1318] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by dodecane iodide to thereby give 3'-dodecylxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-dodecyloxyacetophenone to thereby give (.-.)-N-(1-(3-n-dodecyloxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-68). MS m/z: 509 (M.sup.+).

DETD [1319] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isobutyl iodide to thereby give 3'-isobutoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isobutoxyacetophenone to thereby give (.-.)-N-(1-(3-isobutoxyphenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-69). MS m/z: 397 (M.sup.+).

DETD [1320] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-chlorobenzyl bromide to thereby give 3'-(4-chlorobenzylxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-chlorobenzylxy)acetophenone to thereby give (.-.)-N-(1-(3-(4-chlorobenzylxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (K-2258). MS m/z: 465 (M.sup.+).

DETD [1321] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-chlorobenzyl bromide to thereby give 3'-(2-chlorobenzylxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chlorobenzylxy)acetophenone to thereby give (.-.)-N-(1-(3-(2-chlorobenzylxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-71). MS m/z: 465 (M.sup.+).

DETD [1322] The procedure employed for the synthesis of 3'-ethoxyacetophenone

was repeated but replacing the **ethyl** iodide by benzyl bromide to thereby give 3'-benzyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-benzyloxyacetophenone to thereby give (.-.)-N-(1-(3-benzyloxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-72). MS m/z: 431 (M.sup.+)

DETD [1323] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2,6-dichlorobenzyl bromide to thereby give 3'-(2,6-dichlorobenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2,6-dichlorobenzyl)acetophenone to thereby give (.-.)-N-(1-(3-(2,6-dichlorobenzyl)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-73). MS m/z: 501 (M.sup.+).

DETD [1324] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(6-chlorohexyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(6-chlorohexyl)acetophenone to thereby give (.-.)-N-(1-(3-(6-chlorohexyl)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2260). MS m/z: 459 (M.sup.+).

DETD [1325] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(2-chloroethoxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chloroethoxy)acetophenone to thereby give (.-.)-N-(1-(3-(2-chloroethoxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-75). MS m/z: 403 (M.sup.+).

DETD [1326] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-methylbenzyl bromide to thereby give 3'-(2-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-methylbenzyl)acetophenone to thereby give (.-.)-N-(1-(3-(2-methylbenzyl)phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-76). MS m/z: 445 (M.sup.+).

DETD [1327] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-methylbenzyl bromide to thereby give 3'-(4-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-methylbenzyl)acetophenone to thereby give (.-.)-N-(1-(3-(4-methylbenzyl)phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2268). MS m/z: 445 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylfuran to thereby give (.-.)-N-(1-(2-(5-methyl)furyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-78). MS m/z: 329 (M.sup.+).

DETD [1329] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (.-.)-N-(1-(2-furyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-79). MS m/z: 315 (M.sup.+).

DETD [1330] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-1-methylpyrrole to thereby give (.-.)-N-(1-(2-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-80). MS m/z: 328 (M.sup.+).

DETD [1331] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (.-.)-N-(1-(2-thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-81). MS m/z: 331 (M.sup.+).

DETD [1332] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2,5-dimethylfuran to thereby give (.-.)-N-(1-(3-(2,5-dimethyl)furyl)**ethyl**

)-2-(2',5'-dichlorophenylthio)ethylamine (F-82). MS m/z: 343 (M.sup.+).

DETD [1333] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylthiophene to thereby give (.-)-N-(1-(3-thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-83). MS m/z: 331 (M.sup.+).

DETD [1334] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylthiophene to thereby give (.-)-N-(1-(2-(5-methyl)thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-84). MS m/z: 345 (M.sup.+).

DETD [1335] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-1-methylpyrrole to thereby give (.-)-N-(1-(3-(1-methyl)pyrrolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-85). MS m/z: 329 (M.sup.+).

DETD [1336] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 5-acetyl-2,4-dimethylthiazole to thereby give (.-)-N-(1-(5-(2,4-dimethyl)thiazolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-86). MS m/z: 360 (M.sup.+).

DETD [1337] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the ethyl iodide by cyclohexylmethyl bromide to thereby give 3'-(cyclohexylmethoxybenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(cyclohexylmethoxybenzyloxy)-acetophenone to thereby give (.-)-N-(1-(3-(cyclohexylmethoxybenzyloxy)phenyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-90). MS m/z: 437 (M.sup.+).

DETD [1338] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyridine to thereby give (.-)-N-(1-(2-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-91). MS m/z: 327 (M.sup.+).

DETD [1339] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylpyridine to thereby give (.-)-N-(1-(3-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-92). MS m/z: 326 (M.sup.+).

DETD [1340] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4-acetylpyridine to thereby give (.-)-N-(1-(4-pyridyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-93). MS m/z: 326 (M.sup.+).

DETD [1341] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyrazine to thereby give (.-)-N-(1-(2-pyrazyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-94). MS m/z: 327 (M.sup.+).

DETD [1342] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2-(methylaminesulfonyl)thiophene to thereby give (.-)-N-(1-(3-(2-methylaminosulfonyl)thienyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-95). MS m/z: 425 (M.sup.+).

DETD [1343] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylindole to thereby give (.-)-N-(1-(3-indolyl)ethyl)-2-(2',5'-dichlorophenylthio)ethylamine (F-96). MS m/z 364 (M.sup.+).

DETD . . . was heated under reflux for 30 minutes. Then it was brought back to room temperature and separated into aqueous and ethyl acetate layers. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:ethyl acetate=3:1) to thereby give 510 mg of a bromo compound. This bromo compound (500 mg) was dissolved in acetonitrile (10 ml) and potassium carbonate (763 mg) and (R)-(+)-1-(1-naphthyl)ethylamine (0.18 ml) was added thereto. After further adding tetrabutylammonium iodide (41 mg), the mixture was heated under reflux. After 2 . . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was

purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to thereby give 280 mg of a F-97. MS m/z: 544 (M+1).sup.+.

DETD [1361] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-111. MS m/z: 587 (M+1).sup.+)

DETD [1362] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-112. MS m/z: 601 (M+1).sup.+).

DETD [1363] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-113. MS m/z: 544 (M).sup.+).

DETD [1364] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-114. MS m/z: 628 (M).sup.+).

DETD [1365] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)amine to thereby give F-115. MS m/z: 572 (M).sup.+).

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=363.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=377.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=405.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=419.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=433.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-tert-butylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=447.

CLM What is claimed is:

. . . 14. A method for treating or preventing a disorder selected from the group consisting of hyperparathyroidism, renal osteodystrophy, hypercalcemia malignancy, osteoporosis, Paget's disease and hypertension comprising administering to a patient suffering from said disorder a therapeutically effective amount of a compound, . . .

21. A pharmaceutical composition for treatment of **osteoporosis** comprising a compound, or a pharmaceutically acceptable salt or hydrate thereof, having the formula: wherein: ##STR12## wherein R' and R". .

L2 ANSWER 4 OF 26 USPTAFULL on STN
AN 2003:208165 USPTAFULL
TI Calcium receptor-active compounds
IN Sakai, Teruyuki, Gunma, JAPAN
Takami, Atsuya, Gunma, JAPAN
Nagao, Rika, Gunma, JAPAN
PA NPS Pharmaceuticals, Inc. (non-U.S. corporation)
PI US 2003144526 A1 20030731
AI US 2002-326713 A1 20021219 (10)
RLI Division of Ser. No. US 2002-53133, filed on 17 Jan 2002, PENDING
Continuation of Ser. No. US 1999-214552, filed on 6 Jan 1999, GRANTED,
Pat. No. US 6362231 A 371 of International Ser. No. WO 1997-JP2358,
filed on 8 Jul 1997, UNKNOWN
PRAI JP 1997-107778 19970424
JP 1996-350393 19961227
JP 1996-178315 19960708
DT Utility
FS APPLICATION
LREP NPS PHARMACEUTICALS, INC. C/O FOLEY & LARDNER, P.O. BOX 80278, SAN
DIEGO, CA, 92138-0278
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 51 Drawing Page(s)
LN.CNT 10558
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel calcium receptor active compound having the formula is provided:

Ar.sub.1--[CR.sup.1R.sup.2].sub.p--X--[CR.sup.3R.sup.4].sub.q--
[CR.sup.5R.sup.6]--NR.sup.7--[CR.sup.8R.sup.9]--Ar.sub.2

wherein:

Ar.sub.1 is selected from the group consisting of aryl, heteroaryl,
bis(arylmethyl)amino, bis(heteroarylmethyl)amino and
arylmethyl(heteroarylmethyl)amino;

X is selected from the group consisting of oxygen, sulfur, sulfinyl,
sulfonyl, carbonyl and amino;

R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7, R.sup.8
and R.sup.9 are, for example, hydrogen or alkyl;

Ar.sub.2 is selected from the group consisting of aryl and heteroaryl;

p is an integer of from 0 to 6, inclusive; and,

q is an integer of from 0 to 14, inclusive.

SUMM . . . one or more of the rings has a completely conjugated
pi-electron system. Examples, without limitation, of aryl groups, are
phenyl, **naphthyl**, anthracenyl, phenanthrenyl, fluorenyl, and
indanyl. The aryl group may be substituted or unsubstituted. When
substituted, the substituted group(s) is preferably. . .

SUMM . . . or more halogens and, combined, unsubstituted cycloalkyl and
cycloalkenyl. Also preferably, Ar.sub.1 is selected from the group
consisting of phenyl, **naphthyl**, indolyl, fluorenyl,
dibenzofuranyl, carbazolyl, benzoxazole-2-yl, benzthiazole-2-yl,
pyridin-4-yl, quinolin-2-yl and dibenzylamino and Ar.sub.2 is selected

from the group consisting of phenyl, **naphthyl**, quinolin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrrol-2-yl and pyrrol-3-yl. More preferably, Ar.sub.1 is phenyl substituted with one . . . alkoxy, trihalomethoxy, trihaloacetyl and nitro, and Ar.sub.2 is selected from the group consisting of optionally substituted phenyl and optionally substituted **naphthyl**. Even more preferably, Ar.sub.2 is 3-methoxyphenyl or unsubstituted **naphthyl**. Preferably, R.sup.8 is hydrogen, R.sup.9 is methyl and X is oxygen or sulfur.

SUMM . . . halogen, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, nitro, dimethylamino and unsubstituted phenyl, and optionally substituted **naphthyl**; and Ar.sub.4 is selected from the groups consisting of unsubstituted phenyl, phenyl substituted with one or more groups selected from . . . one or more halogens, unsubstituted lower alkoxy, lower alkoxy substituted with one or more halogens, and halogen, and optionally substituted **naphthyl**.

SUMM . . . substituted with one or more halogens and lower alkoxy substituted with one or more halogens; and Ar.sub.6 is 3-methoxyphenyl or .alpha.-**naphthyl**, more preferably, .alpha.-**naphthyl**. Also preferably, Ar.sub.5 is dibenzylamino, benzyl (**naphthylmethyl**) amino or benzyl(pyridylmethyl)amino optionally substituted with one or more groups independently selected from the group consisting of unsubstituted lower alkyl, . . . lower alkyl substituted with one or more halogens and lower alkoxy substituted with one or more halogens, and Ar.sub.6 is **naphthyl** or methoxyphenyl. More preferably, Ar.sub.5 is dibenzylamino optionally substituted with unsubstituted alkyl, and Ar.sub.6 is .alpha.-**naphthyl**.

SUMM . . . the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (calcimimetic modulation) or blocking the effect of Ca.sup.2+ on a Ca.sup.2+ receptor (**calcilytic** modulation); preferably calcimimetic modulation.

SUMM . . . aspect, the present invention provides a method for the treatment or prevention of primary and secondary hyperparathyroidism, renalosteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension comprising administering a therapeutically effective amount of a compound of this invention to a patient.

SUMM . . . affecting one or more activities of an inorganic ion receptor resulting in a beneficial effect to the patient. For example, **osteoporosis** is an age related disorder characterized by loss of bone mass and increased risk of bone fracture. Compounds blocking osteoclastic . . . levels (e.g., a parathyroid cell ionmimetic). can retard bone loss and, thus, result in beneficial effects to patients suffering from **osteoporosis**.

SUMM . . . increases in parathyroid hormone (e.g., intermittent dosing with a parathyroid cell ionlytic) can increase bone mass in patients suffering from **osteoporosis**.

SUMM . . . modulates one or more effects of an inorganic ion receptor. Inorganic ion receptor modulating agents include ionmimetics, ionlytics, calcimimetics, and **calcilytics**.

SUMM . . . caused by an inorganic ion on an inorganic ion receptor. Preferably, the molecule inhibits one or more calcium receptor activities. **Calcilytics** are ionlytics which inhibit one or more calcium receptor activities evoked by extracellular calcium and preferably bind to a calcium. . .

SUMM . . . preferably a disease or disorder characterized by abnormal calcium homeostasis. Diseases and disorders characterized by abnormal calcium homeostasis include hyperparathyroidism, **osteoporosis**, renalosteodystrophy and other bone and mineral-related disorders, and the like (as described, e.g., in standard medical text books, such as.

. . .

SUMM . . . Such molecules can be used to treat diseases or disorders characterized by abnormal calcium homeostasis such as hyperparathyroidism, renalosteodystrophy and **osteoporosis**.

DETD . . . mimic or block an effect of extracellular Ca.sup.2+ on a calcium receptor. Preferred calcium receptor modulating agents are calcimimetics and **calcilytics**.

DETD [0234] Preferably, the molecule is either a calcimimetic or **calcilytic** having an EC.sub.50 or IC.sub.50 at a calcium receptor of less than or equal to 5 mM, and even more. . .

DETD [0236] In another preferred embodiment the calcium receptor modulating agent is a **calcilytic** which evokes the secretion of parathyroid hormone from parathyroid cells in vitro and elevates the level of parathyroid hormone in. . .

DETD . . . need not possess all the biological activities of extracellular Ca.sup.2+ , but, rather, at least one such activity is mimicked. Similarly, **calcilytics** need not reduce or prevent all of the activities caused by extracellular calcium. Additionally, different calcimimetics and different **calcilytics** do not need to bind to the same site on the calcium receptor as does extracellular Ca.sup.2+ to exert their. . .

DETD [0256] B. **Calcilytics**

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . the reaction mixture was allowed to stand at room temperature and water was added thereto followed by separating extraction with **ethyl** acetate. The organic layer thus obtained was washed with a saturated aqueous solution of sodium chloride and dried over sodium. .

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added

thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was allowed to stand at room temperature and water was added thereto. Then it was subjected to separating extraction with **ethyl** acetate and washed with a saturated aqueous solution of sodium chloride. The organic layer thus obtained was dried over sodium.

DETD . . . was added to the reaction mixture. Then the mixture was stirred at room temperature, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 17.31 g (87.8%) of colorless prism crystals 48.

DETD . . . 6 hours. After the completion of the reaction, the reaction mixture was poured into water under ice-cooling and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, chloroform-**ethyl** acetate) to thereby give 36.8 g (82.8%) of colorless prism crystals 49.

DETD . . . C. for 2.5 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a colorless oil 52.

DETD . . . (0.48 mmol) of the compound 51 in 3 ml of acetonitrile were added 162.7 mg (0.95 mmol, 2.0 moleq.) of (R)-1-(1-naphthyl)ethylamine and 131.3 mg (0.95 mmol, 2.0 moleq.) of potassium carbonate and the resulting mixture was stirred under heating at an. . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . . for 2 hours. After the completion of the reaction, the reaction mixture was concentrated, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 122.6 mg (93.8%) of a

colorless oil 53.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 723.4 mg (87.0%) of a colorless oil 55.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 56.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 202.4 mg (73.3%) of a colorless prism crystals 58.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 216.6 mg (88.0%) of a colorless oil 59.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 824.0 mg (84.9%) of a colorless oil 61.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 222.6 mg (87.1%) of a colorless oil 62.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 884.2 mg (91.1%) of a colorless oil 64.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the

obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 229.3 mg (89.7%) of a colorless oil 65.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 876.5 mg (90.3%) of a colorless oil 67.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 293.1 mg (87.2%) of a colorless oil 68.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 804.3 mg (77.0%) of colorless prism crystals 70.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 880.8 mg (89.5%) of a colorless oil 71.

DETD . . . temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 551.8 mg (100%) of a colorless oil 73.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 230.8 mg (91.3%) of a colorless oil 74.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, ethyl acetate-n-hexane) to thereby give 241.3 mg (45.9%) of a colorless oil 76.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a

saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 209.8 mg (69.7%) of a colorless oil 77.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 586 mg (61.4%) of a colorless oil 79.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 265.1 mg (82.8%) of a colorless oil 80.

DETD . . . C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 564.9 mg (82.5%) of colorless prism crystals 82.

DETD . . . 60.degree. C. for 4 hours. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, **ethyl** acetate-n-hexane) to thereby give 311.9 mg (83.8%) of colorless prism crystals 83.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 85.

DETD . . . acidified with a 5% aqueous solution of hydrochloric acid. Then the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 790.0 mg (98.4%) of colorless prism crystals 86.

DETD . . . temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-**ethyl** acetate) to thereby give 615.4 mg (98.5%) of colorless prism crystals 87.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with **ethyl** acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with

water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 76.3 mg (82.6%) of a colorless oil 88.

DETD [0389] To a solution of 600 mg (3.5 mmol) of (R)-1-(1-naphthyl)ethylamine 89 in 5 ml of methylene chloride were added 580.3 mg (d=1.176, 3.85 mmol, 1.1 moleq.) of ethylmalonyl chloride and . . . and dried over sodium sulfate. After distilling off the solvent, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 662.9 mg (66.5%) of colorless prism crystals 90.

DETD . . . concentrated, acidified with a 5% aqueous solution of hydrochloric acid. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of sodium . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 596.0 mg (99.8%) of colorless prism crystals 91.

DETD . . . (1.56 mmol) of the compound 91 in 5 ml of dimethylformamide were added 293.2 mg (1.71 mmol, 1.1 moleq.) of (R)-1-(1-naphthyl)ethylamine and 359.2 mg (1.87 mmol, 1.2 moleq.) of WSC.times.HCl and the resulting mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained crystals were purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 615.1 mg (96.4%) of colorless prism crystals 92.

DETD . . . the reaction mixture was poured into water, acidified with a 5% aqueous solution of hydrochloric acid and then extracted with ethyl acetate. The hydrochloric acid layer was made alkaline by adding a 5% aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography (silica gel, n-hexane-ethyl acetate) to thereby give 82.0 mg (88.0%) of a colorless oil 93.

DETD [0398] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 361.8 mg (80.0%) of the compound 102 as colorless prisms.

DETD . . . a solution of the above compound 102 (125.8 mg, 0.38 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0402] After the completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, ethyl acetate/n-hexane] to thereby give 67.1 mg (89.5%) of the compound 103 as a colorless oil.

DETD [0406] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, n-hexane/**ethyl** acetate] to thereby give the compound 105 (723.4 mg, 87.0%) as a colorless oil.

DETD . . . a solution of the above compound 105 (106.2 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (48.4 mg, 0.35 mmol, 1.2 mol eq.) and the resulting mixture was stirred. . .

DETD [0409] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 33.7 mg (76.1%) of the compound 106 as a colorless oil.

DETD [0413] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 804.3 mg (77.0%) of the compound 108 as colorless prisms.

DETD . . . a solution of the above compound 108 (106.9 mg, 0.35 mmol, 1.2 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) and potassium carbonate (60.5 mg, 0.44 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0416] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 67.2 mg (58.3%) of the compound 109 as a colorless oil.

DETD [0420] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 586 mg (61.4%) of the compound 111 as a colorless oil.

DETD . . . a solution of the above compound 111 (65.3 mg, 0.26 mmol, 1.5 mol eq.) in acetonitrile (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (29.3 mg, 0.17 mmol) and potassium carbonate (35.5 mg, 0.26 mmol, 1.5 mol eq.) and the resulting mixture was stirred. . .

DETD [0424] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The residue thus obtained was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 36.5 mg (62.0%) of the compound 112 as a colorless oil.

DETD [0427] To a solution of (R)-(+)-1-(1-**naphthyl**)ethylamine (600 mg, 3.5 mmol) in dichloromethane (5 ml) were added ethylmalonyl chloride

113 (580.3 mg, 3.85 mmol, 1.1 mol eq.). . .

DETD . . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 662.9 mg (66.5%) of the compound 114 as colorless prisms.

DETD . . . the reaction mixture was concentrated, acidified with a 5% aqueous solution of hydrochloric acid, poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed successively with a 5% aqueous solution of hydrochloric acid, water and a saturated aqueous solution of. . . sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 659.5 mg of the compound 115 as colorless prisms.

DETD [0435] To a solution of the above compound 115 (50 mg, 0.19 mmol) in N,N-dimethylformamide (3 ml) were added (R)-(+)-1-(1-**naphthyl**)ethylamine (45.0 mg, 0.21 mmol, 1.1 mol eq.) and WSC HCl (44.9 mg, 0.23 mmol, 1.2 mol eq.) and the resulting mixture. . .

DETD [0436] After the completion of the reaction, the reaction mixture was poured into water and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride. After drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 61.6 mg (70.5%) of the compound 116 as colorless prisms.

DETD . . . into the reaction mixture. Then the mixture was acidified with a 5% aqueous solution of hydrochloric acid and extracted with **ethyl** acetate. The layer of the 5% aqueous solution of hydrochloric acid was made alkaline by adding a 5% aqueous solution of sodium hydroxide and then extracted with **ethyl** acetate. After washing with water and a saturated aqueous solution of sodium chloride and drying over sodium sulfate, the solvent was distilled off under reduced pressure. The crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 18.0 mg (88.0%) of the compound 117 as a colorless oil.

DETD . . . After the completion of the reaction, ammonium chloride was added thereto in excess and the reaction mixture was extracted with **ethyl** acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After distilling off the solvent under reduced pressure, the crystals thus obtained were purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 16.0 g of the compound 119.

DETD [0447] After cooling by allowing to stand, it was purified by column chromatography and eluted with **ethyl** acetate/n-hexane to thereby give 700 mg of the compound 120.

DETD . . . sodium sulfate. After distilling off the solvent under reduced pressure, the obtained residue was purified by column chromatography [silica gel, **ethyl** acetate/n-hexane] to thereby give 1.5 g of the compound 122.

DETD [0454] The above compound 122 (150 mg, 0.51 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (104.5 mg, 0.61 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (3 ml) and then allowed to stand at room. . .

DETD Synthesis of K-2027 (N-{5-[(4-chlorophenyl)thio]pentyl}-N-[(1R)-1-(1-**naphthyl**)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (241 mg, 1.74 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.31 ml, 1.92 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . C. for 24 hours. After confirming the completion of the reaction by TLC, potassium carbonate (1.70 g, 12.3 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.45 ml, 2.79 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2052 (N-[5-[(4-fluorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (210 mg, 1.52 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (300 mg, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (247 mg, 1.79 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2076 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[4-(trifluoromethyl)phenyl]thio]pentyl)amine)

DETD . . . temperature for 1 hour. After confirming the completion of the reaction by TLC, potassium carbonate (200 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.28 ml, 1.73 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2087 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[3-(trifluoromethyl)phenyl]thio]butyl)amine)

DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (300 mg, 2.17 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.30 ml, 1.86 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD Synthesis of K-2117 ((R)-N-[1-(1'-naphthyl)ethyl]-2-(2',5'-dichlorophenylthio)ethylamine)

DETD . . . ice-cooling for 2 hours. After confirming the completion of the reaction by TLC, potassium carbonate (4.0 g, 28.9 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (3.70 ml, 22.9 mmol) were added at room temperature to the reaction system and the resulting mixture was stirred at. . .

DETD [0594] The compound thus obtained (50 mg, 0.20 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (41.0 mg, 0.24 mmol, 1.2 mol eq.) were dissolved in chloroform-methanol (2 ml) and allowed to stand at room temperature. . .

DETD Synthesis of K-2246 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[4-(trifluoromethyl)phenyl]thio]butyl)amine)

DETD . . . reaction by TLC, 5 ml of acetonitrile, 693 mg (5.01 mmol) of potassium carbonate and 0.49 ml (2.96 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD . . . reaction by TLC, 8 ml of acetonitrile, 853 mg (6.17 mmol) of potassium carbonate and 0.60 ml. (3.63 mmol) of (R)-(+)-1-(1-naphthyl)ethylamine were added thereto at room temperature and the obtained mixture was stirred at 85.degree. C. for 12 hours.

DETD Synthesis of K-2243 (N1,N1-di(4-chlorobenzyl)-3-[(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD [0606] After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue, and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0610] 100 mg (0.31 mmol) of the above-mentioned compound 125 and 64.2 mg (0.38 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2257 (N1,N1-di[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0616] 450 mg (1.07 mmol) of the above-mentioned compound 127 and 220.7 mg (1.29 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4: 1) and allowed to stand at room temperature for 1 week. After the completion of. . .

DETD Synthesis of K-2259 (N1,N1-di[4-(trifluoromethyl)benzyl]-3-([(1 R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . at room temperature for 12 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. Ethyl acetate and water were poured into the residue and filtered through celite. The residue was washed with ethyl acetate and then the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After. . .

DETD [0622] 800 mg (2.06 mmol) of the above-mentioned compound 129 and 424.0 mg (2.48 mmol, 1.2 mol eq.) of (R)-(+)-(1-naphthyl)ethylamine were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After the completion of the. . .

DETD Synthesis of K-2247 (N1-benzyl-N1-(4-chlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0626] The conjugated ketone compound 202 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0630] The conjugated ketone compound 204 (105.8 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-naphthyl)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the

washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0634] The conjugated ketone compound 206 (100.3 mg, 0.35 mmol, 1.2 mol eq.) and (R)-(+)-1-(1-**naphthyl**)ethylamine (50 mg, 0.29 mmol) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1 week. After. . .

DETD Synthesis of K-2250 (N1-benzyl-N1-(3,4-dichloro-benzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**amino]propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0638] The conjugated ketone compound 208 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0642] The conjugated ketone compound 210 (1 00 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and the. . .

DETD [0646] The conjugated ketone compound 212 (100 mg, 0.35 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (71.8 mg, 0.42 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0650] The conjugated ketone compound 214 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the

washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0654] The conjugated ketone compound 216 (100 mg, 0.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (64.2 mg, 0.38 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0658] The conjugated ketone compound 218 (800 mg, 1.63 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (33.7 mg, 1.95 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0662] The conjugated ketone compound 220 (1 g, 3.13 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (642.2 mg, 3.75 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2262 (N1-(2-chlorobenzyl)-N1-(4-chlorobenzyl)-3-(((1R)-1-(1-**naphthyl**)ethyl)amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0666] The conjugated ketone compound 222 (500 mg, 1.56 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (321.1 mg, 1.88 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 1. . .

DETD Synthesis of K-2264 (N1-(3,4-dichlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-(((1R)-1-(1-**naphthyl**)ethyl)amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0672] The conjugated ketone compound 224 (800 mg, 2.06 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (387.7 mg, 2.26 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2265 (N1,N1-di(3,4-dichlorobenzyl)-3-(((1R)-1-(1-

naphthyl)ethyl]amino)propanamide)

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 225 (71.2.2 mg, 74.3%).

DETD [0678] The conjugated ketone compound 226 (280 mg, 0.72 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (148 mg, 0.864 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2266 (N1-(4-chlorobenzyl)-N1-[(4-trifluoromethyl)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0684] The conjugated ketone compound 228 (800 mg, 2.26 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (425.4 mg, 2.48 mmol, 1.1 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2267 (N1-(4-chlorobenzyl)-N1-(3,4-dichlorobenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . .

DETD [0690] The conjugated ketone compound 230 (600 mg, 1.69 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (347.2 mg, 2.03 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2270 (N1,N1-di(4-methoxybenzyl)-3-([(1R)-1-(1-naphthyl)ethyl]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added ethyl acetate and water and the mixture was filtered through celite. The residue was washed with ethyl acetate and the washing liquor was combined with the filtrate and extracted with ethyl acetate. The ethyl acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . .

DETD [0696] The conjugated ketone compound 232 (450 mg, 1.45 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (297 mg, 1.74 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2272 (N1-(3,4-dichlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography (silica gel, hexane : ethyl acetate (9:1-4:1)] to thereby give a colorless oil 233 (777.3 mg, 78.2%).

DETD [0702] The conjugated ketone compound 234 (350 mg, 0.87 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (178 mg, 1.04 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2283 (N1-(4-chlorobenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-naphthyl)ethyl]-amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil

thus obtained was purified by column chromatography [silica gel, hexane **ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 235 (1.092 g, 98.1%).

DETD [0708] The conjugated ketone compound 236 (400 mg, 1.08 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (222 mg, 1.30 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature. . . .

DETD Synthesis of K-2289 (N1-(4-chlorobenzyl)-N1-(4-methoxybenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane **ethyl** acetate (9:1-4:1)] to thereby give a colorless oil 237 (711.8 mg, 74.8%).

DETD [0714] The conjugated ketone compound 238 (414 mg, 1.31 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (270 mg, 1.57 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for 12. . . .

DETD Synthesis of K-2290 (N1-(4-methoxybenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . . .

DETD [0720] The conjugated ketone compound 240 (874.7 mg, 2.50 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (513.9 mg, 3.00 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . . .

DETD Synthesis of K-2291 (N1-(4-chlorobenzyl)-N1-(2-naphthylmethyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. To the obtained residue were added **ethyl** acetate and water and the mixture was filtered through celite. The residue was washed with **ethyl** acetate and the washing liquor was combined with the filtrate and extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with water and a saturated aqueous solution of sodium chloride and dried over sodium sulfate and. . . .

DETD [0726] The conjugated ketone compound 242 (500 mg, 1.49 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (307 mg, 1.79 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . . .

DETD Synthesis of K-2294 (N1-(3,4-dichlorobenzyl)-N1-(4-methylbenzyl)-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . . .

DETD [0732] The conjugated ketone compound 244 (1.5587 g, 4.67 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (959.6 mg, 5.60 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . . .

DETD Synthesis of K-2299 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethyl)benzyl]-3-([(1R)-1-(1-**naphthyl**)**ethyl**]amino)propanamide)

DETD . . . After the completion of the reaction, the solvent was distilled off under reduced pressure. The obtained residue was extracted with **ethyl** acetate. The **ethyl** acetate layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium. . . .

DETD [0738] The conjugated ketone compound 246 (1.4568 g, 4.36 mmol) and

(R)-(+)-1-(1-**naphthyl**)ethylamine (896.8 mg, 5.24 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2300 (N1,N1-di(4-methylbenzyl)-3-([(1R)-1-(1-**naphthyl**)ethyl]amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 247 (819.4 mg, 88.2%).

DETD [0744] The conjugated ketone compound 248 (400 mg, 1.43 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (295 mg, 1.72 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2309 (N1-(3,4-dichlorobenzyl)-N1-(4-methoxybenzyl)-3-([(1R)-1-(1-**naphthyl**)ethyl]amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 249 (827.0 mg, 76.8%).

DETD [0750] The conjugated ketone compound 250 (692.4 mg, 1.98 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (407 mg, 2.37 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2310 (N1-(4-methylbenzyl)-N1-[4-(trifluoromethoxy)benzyl]-3-([(1R)-1-(1-**naphthyl**)ethyl]amino)propanamide)

DETD . . . the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography [silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 251 (979.1 mg, 80.4%).

DETD [0756] The conjugated ketone compound 252 (685.1 mg, 1.96 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (403 mg, 2.36 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD . . . and the solvent was distilled off under reduced pressure. The oil thus obtained was purified by column chromatography (silica gel, hexane:ethyl acetate (9:1-4:1)] to thereby give a colorless oil 253 (944.0 mg, 83.4%).

DETD [0762] The conjugated ketone compound 254 (612.8 mg, 1.68 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (345 mg, 2.01 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD [0768] The conjugated ketone compound 256 (260.2 mg, 0.88 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (180 mg, 1.05 mmol, 1.2 mol eq.) were dissolved in chloroform/methanol (4:1) and allowed to stand at room temperature for. . .

DETD Synthesis of K-2280 (N-[5-[(4-methoxyphenyl)thio]pentyl]-N-[(1R)-1-(1-**naphthyl**)ethyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (931 mg, 6.75 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.52 ml, 3.22 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2281 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-[4-[(2,4,5-trichlorophenyl)thio]butyl]amine)

DETD . . . temperature for 3 hours. After confirming the completion of the reaction by TLC, potassium carbonate (545 mg, 3.94 mmol) and (R)-(+)-1-(1-**naphthyl**)ethylamine (0.41 ml, 3.94 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

DETD Synthesis of K-2282 (N-[(1R)-1-(1-**naphthyl**)ethyl]-N-[5-[(2,4,5-trichlorophenyl)thio]pentyl]amine)

DETD . . . temperature for 2.5 hours. After confirming the completion of

the reaction by TLC, potassium carbonate (1.00 g, 7.25 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.69 ml, 4.27 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .

- DETD Synthesis of K-2287 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[4-(trifluoromethoxy)phenyl]thio]butyl)amine)
DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (710 mg, 5.14 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.53 ml, 3.28 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .
- DETD Synthesis of K-2288 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[4-(trifluoromethoxy)phenyl]thio]pentyl)amine)
DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (770 mg, 5.57 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.58 ml, 3.59 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .
- DETD Synthesis of K-2293 (N-{4-[(4-chlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD . . . temperature for 5 hours. After confirming the completion of the reaction by TLC, potassium carbonate (775 mg, 5.61 mmol) and (R)-(+)-1-(1-naphthyl)ethylamine (0.62 ml, 3.84 mmol) were added at the same temperature to the reaction system. Further, the reaction mixture was stirred. . .
- DETD Synthesis of K-2240 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(3-[[4-(trifluoromethyl)phenyl]thio]propyl)amine)
DETD Synthesis of K-2263 (N-{4-[(4-fluorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2269 (N-{4-[(3-methoxyphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2271 (N-[[4-(5-ethoxy-1,3-benzothiazol-2-yl)thio]butyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2279 (N-[[5-(3-methoxyphenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2284 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(5-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]pentyl)amine)
DETD Synthesis of K-2286 (N-{6-[(4-chlorophenyl)thio]hexyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2292 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(7-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]heptyl)amine)
DETD Synthesis of K-2296 (N-[[5-(2,5-dichlorophenyl)thio]pentyl]-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2297 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(4-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]thio]butyl)amine)
DETD Synthesis of K-2298 (N-{4-[(2,5-dichlorophenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2301 (N-[(1R)-1-(1-naphthyl)ethyl]-N-(6-[[4-(trifluoromethoxy)phenyl]thio]hexyl)amine)
DETD Synthesis of K-2302 (N-{4-[(2,4-dimethylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2303 (N-{5-[(2,4-dimethylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2304 (N-{4-[(4-methylphenyl)thio]butyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD Synthesis of K-2305 (N-{5-[(4-methylphenyl)thio]pentyl}-N-[(1R)-1-(1-naphthyl)ethyl]amine)
DETD . . . crystals by the same method as the one employed for the synthesis of K-2293 but replacing the 4-chlorothiophenol,

1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine respectively by 3-trifluoromethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-methylbenzylamine. m/z=355.

DETD . . . synthesized by almost the same method as the one employed for the synthesis of S-1 but replacing the (R)-(+)-3-methoxy-.alpha.-benzylmethylamine by (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z =419.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=349.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,6-dimethylthiophenol and

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl) ethylamine.

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α .benzylmethylamine respectively by 2,6-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

... method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 3,4-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

$m/z=391.$

2.5. . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 3,4-dimethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

... method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 3,5-dimethylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.

one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 3,5-dimethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=398.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-chloro-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=444, 446.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrachloro-4-mercaptopyridine, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=447.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-

trifluoromethylthiophenol, 1,10-dibromodecane and (R)-(+)-1-(1-naphthyl)ethylamine.

- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,3,5,6-tetrafluoro-4-trifluoromethylthiophenol, 1,12-dibromododecane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-isopropylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4,5-trichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.
- DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=408.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=422.
- DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-

.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 6-ethoxy-2-mercaptobenzothiazole, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=375.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,4-dichlorothiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2,5-dichlorothiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-naphthyl)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol and (R)-(+)-1-(1-naphthyl)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol,

1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-trifluoromethoxythiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=355.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-chlorobenzylmercaptan, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 2-quinolinethiol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 4-methylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=424.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy-.alpha.-benzylmethylamine respectively by 5-fluoro-2-mercaptobenzothiazole, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=438.

DETD . . . potassium carbonate (4.04 g) was added thereto. After 1 hour, water was added and the resulting mixture was extracted with **ethyl** acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crystals thus obtained were washed with chloroform to thereby give N-(2-(2',5'-dichlorophenylthio)**ethyl**)phthalimide (F-8) (8.28 g). MS m/z:351 (M.sup.+).

DETD [1327] N-(2-(2',5'-Dichlorophenylthio)**ethyl**)phthalimide (F-8) (7.06 g) was added to ethanol (120 ml). After further adding hydrazine monohydrate (6.9 ml), the obtained mixture was. . .

DETD . . . ice-cooling. Then the mixture was brought to room temperature and stirred for 15 hours. The reaction mixture was concentrated and **ethyl** acetate and water were added thereto. The insoluble matters were filtered off and the organic layer was washed with a. . . sulfate, filtered and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, chloroform/methanol=50:1) to thereby give (.-.-)-N-(1-(3-methoxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-12) (146 mg). MS m/z: 355 (M.sup.+).

DETD [1329] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethoxyacetophenone to thereby give (.-.-)-N-(1-(3,4-dimethoxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 385 (M.sup.+).

DETD [1330] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-methylacetophenone to thereby give (.-.-)-N-(1-(3-methylphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-14). MS m/z: 339 (M.sup.+).

DETD [1331] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-methylacetophenone to thereby give (.-.-)-N-(1-(4-methylphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-13). MS m/z: 339 (M.sup.+).

DETD [1332] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4',5'-trimethoxyacetophenone to thereby give (.-.-)-N-(1-(3,4,5-trimethoxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-16). MS m/z: 415 (M.sup.+).

DETD [1333] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxyacetophenone to thereby give (.-.-)-N-(1-(4-hydroxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-17). MS m/z: 341 (M.sup.+).

DETD [1334] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethyl)acetophenone to thereby give (.-.-)-N-(1-(3-trifluoromethylphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-18). MS m/z: 393 (M.sup.+).

DETD [1335] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-hydroxy-3'-methoxyacetophenone to thereby give (.-.-)-N-(1-(4-hydroxy-3-methoxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-21). MS m/z: 371 (M.sup.+).

DETD [1336] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-bromoacetophenone to thereby give (.-.-)-N-(1-(4-bromophenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-22). MS m/z: 405 (M.sup.+).

DETD [1337] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-bromoacetophenone to thereby give (.-.-)-N-(1-(3-bromophenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-23). MS m/z: 405 (M.sup.+).

DETD [1338] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-bromoacetophenone to thereby give (.-.-)-N-(1-(2-bromophenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-24). MS m/z: 405 (M.sup.+).

DETD [1339] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dihydroxyacetophenone to thereby give (.-.-)-N-(1-(3,4-dihydroxyphenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-29). MS m/z: 357 (M.sup.+).

DETD [1340] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dichloroacetophenone to thereby give (.-.-)-N-(1-(2,5-chlorophenyl)**ethyl**)
)-2-(2',5'-dichlorophenylthio)ethylamine (F-30). MS m/z: 395 (M.sup.+).

DETD [1341] The procedure employed for the synthesis of F-12 was repeated but

replacing the 3'-methoxyacetophenone by 3'-fluoro-4'-methoxyacetophenone to thereby give (.+-.)-N-(1-(3-fluoro-4-methoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-31). MS m/z: 373 (M.sup.+).

DETD [1342] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(trifluoromethoxy)acetophenone to thereby give (.+-.)-N-(1-(3-trifluoromethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-35). MS m/z: 409 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dimethylacetophenone to thereby give (.+-.)-N-(1-(3,4-dimethylphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-48). MS m/z: 353 (M.sup.+).

DETD [1344] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2'-chloroacetophenone to thereby give (.+-.)-N-(1-(2-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-49). MS m/z: 359 (M.sup.+).

DETD [1345] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-chloroacetophenone to thereby give (.+-.)-N-(1-(3-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-50). MS m/z: 359 (M.sup.+).

DETD [1346] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-chloroacetophenone to thereby give (.+-.)-N-(1-(4-chlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-51). MS m/z: 359 (M.sup.+).

DETD [1347] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-fluoroacetophenone to thereby give (.+-.)-N-(1-(3-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-52). MS m/z: 343 (M.sup.+).

DETD [1348] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4'-fluoroacetophenone to thereby give (.+-.)-N-(1-(4-fluorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-53). MS m/z: 343 (M.sup.+).

DETD [1349] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',5'-dimethylacetophenone to thereby give (.+-.)-N-(1-(2,5-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-54). MS m/z: 353 (M.sup.+).

DETD [1350] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dimethylacetophenone to thereby give (.+-.)-N-(1-(2,4-dimethylphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-55). MS m/z: 353 (M.sup.+).

DETD [1351] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2',4'-dichloroacetophenone to thereby give (.+-.)-N-(1-(2,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-57). MS m/z: 395 (M.sup.+).

DETD [1352] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3',4'-dichloroacetophenone to thereby give (.+-.)-N-(1-(3,4-dichlorophenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-58). MS m/z: 395 (M.sup.+).

DETD [1353] 3'-Hydroxyacetophenone (200 mg) was dissolved in acetonitrile (4 ml). After adding **ethyl** iodide (0.2 ml) and potassium carbonate (347 mg), the mixture was stirred at 70.degree. C. for 9 hours. After 9 hours, water and **ethyl** acetate were added to the reaction mixture followed by separation. The organic layer was washed with a saturated aqueous solution. . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane: **ethyl** acetate=8:1) to thereby give 204 mg of 3'-ethoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated, but replacing the 3'-methoxyacetophenone by 3'-ethoxyacetophenone to thereby give (.+-.)-N-(1-(3-ethoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-63). MS m/z : 369 (M.sup.+).

DETD [1354] The procedure employed for the synthesis of 3'-ethoxyacetophenone

was repeated but replacing the **ethyl** iodide by n-propyl iodide to thereby give 3'-n-propoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-propoxyacetophenone to thereby give (.-)-N-(1-(3-n-propoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-64). MS m/z: 383 (M.sup.+).

DETD [1355] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-butyl iodide to thereby give 3'-n-butoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-butoxyacetophenone to thereby give (.-)-N-(1-(3-n-butoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-65). MS m/z : 397 (M.sup.+).

DETD [1356] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by n-hexyl bromide to thereby give 3'-n-hexyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-hexyloxyacetophenone to thereby give (.-)-N-(1-(3-n-hexyloxyphenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2255). MS m/z: 425 (M.sup.+).

DETD [1357] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isopropyl iodide to thereby give 3'-isopropoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isopropoxyacetophenone to thereby give (.-)-N-(1-(3-isopropoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-67). MS m/z: 383 (M.sup.+).

DETD [1358] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by dodecane iodide to thereby give 3'-dodecyl,xyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-n-dodecyloxyacetophenone to thereby give (.-)-N-(1-(3-n-dodecyloxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-68). MS m/z: 509 (M.sup.+).

DETD [1359] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by isobutyl iodide to thereby give 3'-isobutoxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-isobutoxyacetophenone to thereby give (.-)-N-(1-(3-isobutoxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-69). MS m/z: 397 (M.sup.+).

DETD [1360] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-chlorobenzyl bromide to thereby give 3'-(4-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-chlorobenzoyloxy)acetophenone to thereby give (.-)-N-(1-(3-(4-chlorobenzoyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2258). MS m/z: 465 (M.sup.+).

DETD [1361] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-chlorobenzyl bromide to thereby give 3'-(2-chlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chlorobenzoyloxy)acetophenone to thereby give (.-)-N-(1-(3-(2-chlorobenzoyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-71). MS m/z: 465 (M.sup.+).

DETD [1362] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by benzyl bromide to thereby give 3'-benzyloxyacetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-benzyloxyacetophenone to thereby give (.-)-N-(1-(3-benzyloxyphenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine

(F-72). MS m/z: 431 (M.sup.+).

DETD [1363] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2,6-dichlorobenzyl bromide to thereby give 3'-(2,6-dichlorobenzoyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2,6-dichlorobenzoyloxy)acetophenone to thereby give (.+-.)-N-(1-(3-(2,6-dichlorobenzoyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-73). MS m/z :501 (M.sup.+).

DETD [1364] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(6-chlorohexyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(6-chlorohexyloxy)acetophenone to thereby give (.+-.)-N-(1-(3-(6-chlorohexyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2260). MS m/z: 459 (M.sup.+).

DETD [1365] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 1-bromo-6-chlorohexane to thereby give 3'-(2-chloroethoxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-chloroethoxy)acetophenone to thereby give (.+-.)-N-(1-(3-(2-chloroethoxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-75). MS m/z: 403 (M.sup.+).

DETD [1366] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 2-methylbenzyl bromide to thereby give 3'-(2-methylbenzyl)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(2-methylbenzyl)acetophenone to thereby give (.+-.)-N-(1-(3-(2-methylbenzyl)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-76). MS m/z: 445 (M.sup.+).

DETD [1367] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by 4-methylbenzyl bromide to thereby give 3'-(4-methylbenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(4-methylbenzyloxy)acetophenone to thereby give (.+-.)-N-(1-(3-(4-methylbenzyloxy)phenyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (K-2268). MS m/z: 445 (M.sup.+).

DETD [1368] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylfuran to thereby give (.+-.)-N-(1-(2-(5-methyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-78). MS m/z: 329 (M.sup.+).

DETD [1369] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (.+-.)-N-(1-(2-furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-79). MS m/z: 315 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-1-methylpyrrole to thereby give (.+-.)-N-(1-(2-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-80). MS m/z: 328 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylthiophene to thereby give (.+-.)-N-(1-(2-thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-81). MS m/z: 331 (M.sup.+).

DETD [1372] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2,5-dimethylfuran to thereby give (.+-.)-N-(1-(3-(2,5-dimethyl)furanyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-82). MS m/z: 343 (M.sup.+).

DETD [1373] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylthiophene to thereby give (.+-.)-N-(1-(3-thienyl)**ethyl**)-2-(2',5'-

dichlorophenylthio)ethylamine (F-83). MS m/z: 331 (M.sup.+).

DETD [1374] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetyl-5-methylthiophene to thereby give (.-.-)-N-(1-(2-(5-methyl)thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-84). MS m/z: 345 (M.sup.+).

DETD [1375] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-1-methylpyrrole to thereby give (.-.-)-N-(1-(3-(1-methyl)pyrrolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-85). MS m/z: 329 (M.sup.+).

DETD [1376] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 5-acetyl-2,4-dimethylthiazole to thereby give (.-.-)-N-(1-(5-(2,4-dimethyl)thiazolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-86). MS m/z: 360 (M.sup.+).

DETD [1377] The procedure employed for the synthesis of 3'-ethoxyacetophenone was repeated but replacing the **ethyl** iodide by cyclohexylmethyl bromide to thereby give 3'-(cyclohexylmethoxybenzyloxy)acetophenone. The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3'-(cyclohexylmethoxybenzyloxy)-acetophenone to thereby give (.-.-)-N-(1-(3-(cyclohexylmethoxybenzyloxy) phenyl) **ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-90). MS m/z: 437 (M.sup.+).

DETD [1378] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyridine to thereby give (.-.-)-N-(1-(2-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-91). MS m/z: 327 (M.sup.+).

DETD . . . The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylpyridine to thereby give (.-.-)-N-(1-(3-pyridyl) **ethyl**)-2-(2',5'-dichlorophenylthio) ethylamine (F-92). MS m/z: 326 (M.sup.+).

DETD [1380] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 4-acetylpyridine to thereby give (.-.-)-N-(1-(4-pyridyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-93). MS m/z: 326 (M.sup.+).

DETD [1381] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 2-acetylpyrazine to thereby give (.-.-)-N-(1-(2-pyrazyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-94). MS m/z: 327 (M.sup.+).

DETD [1382] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetyl-2-(methylaminesulfonyl)thiophene to thereby give (.-.-)-N-(1-(3-(2-methylaminosulfonyl)thienyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-95). MS m/z: 425 (M.sup.+).

DETD [1383] The procedure employed for the synthesis of F-12 was repeated but replacing the 3'-methoxyacetophenone by 3-acetylindole to thereby give (.-.-)-N-(1-(3-indolyl)**ethyl**)-2-(2',5'-dichlorophenylthio)ethylamine (F-96). MS m/z: 364 (M.sup.+).

DETD . . . was heated under reflux for 30 minutes. Then it was brought back to room temperature and separated into aqueous and **ethyl** acetate layers. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=3:1) to thereby give 510 mg of a bromo compound. This bromo compound (500 mg) was dissolved in acetonitrile (10 ml) and potassium carbonate (763 mg) and (R)-(+)-1-(1-naphthyl)ethylamine (0.18 ml) was added thereto. After further adding tetrabutylammonium iodide (41 mg), the mixture was heated under reflux. After 2 . . . sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product thus obtained was purified by silica gel chromatography (n-hexane:**ethyl** acetate=2:1) to thereby give 280 mg of a F-97. MS m/z: 544 (M+1.sup.+).

DETD [1398] The procedure employed for the synthesis of F-99 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-

trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-111. MS m/z: 587 (M+1.sup.+).

DETD [1399] The procedure employed for the synthesis of F-103 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-112. MS m/z: 601 (M+1.sup.+).

DETD [1400] The procedure employed for the synthesis of F-97 was repeated but replacing the di(4-trifluoromethyl)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-113. MS m/z: 544 (M.sup.+).

DETD [1401] The procedure employed for the synthesis of F-108 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-114. MS m/z: 628 (M.sup.+).

DETD [1402] The procedure employed for the synthesis of F-102 was repeated but replacing the di(4-trifluoromethoxy)benzylamine by N-(4-trifluoromethylbenzyl)-N-(3,4-dichlorobenzyl)**amine** to thereby give F-115. MS m/z: 572 (M.sup.+).

DETD . . . method as the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=363.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,3-dibromopropane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=377.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,4-dibromobutane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=391.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,5-dibromopentane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=405.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,6-dibromohexane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=419.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,7-dibromoheptane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=433.

DETD . . . the one employed for the synthesis of S-1 but replacing the 2,5-dimethylthiophenol, 1-bromo-2-chloroethane and (R)-(+)-3-methoxy- α -benzylmethylamine respectively by 4-tert-butylthiophenol, 1,8-dibromooctane and (R)-(+)-1-(1-**naphthyl**)ethylamine. m/z=447.

CLM What is claimed is:

- . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or α -**naphthyl**; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the . . .
- . . . substituted with one or more groups independently selected from the group consisting of halogen, or lower alkoxy; Ar.sub.6 is unsubstituted **naphthyl**; R.sup.17 is H or methyl; R.sup.18 is methyl; W is sulfur, sulfinyl, or sulfonyl; t is 0; u is 1.
- . . .

- . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . activities in a cell treats or prevents a disorder selected from the group consisting of hyperparathyroidism, renal osteodystrophy, hypercalcemia malignancy, **osteoporosis**, Paget's disease and hypertension.
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
 - . . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .
86. (New) A pharmaceutical composition for treatment of **osteoporosis** comprising a compound, or a pharmaceutically acceptable salt or hydrate thereof, having the formula:
 Ar.sub.5--[CH(R.sup.16)].sub.t--W--(CH.sub.2).sub.u--CHR.sup.17)--NH--CH(R.sup.18)--Ar wherein: Ar.sub.5 is phenyl, indole,. . . more halogens, lower alkoxy substituted with one or more halogens, nitro, dimethylamino, and unsubstituted phenyl; Ar.sub.6 is 3-methoxy phenyl or alpha-naphthyl; t is 0 or 1; u is an integer of from 0 to 11, inclusive; W is selected from the. . .

L2 ANSWER 5 OF 26 USPATFULL on STN

AN 2003:47795 USPATFULL

TI **Calcilytic** compounds

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PI US 6521667 B1 20030218
AI US 1998-132179 19980811 (9)
RLI Division of Ser. No. US 1997-832984, filed on 4 Apr 1997, now patented, Pat. No. US 6022894 Continuation-in-part of Ser. No. US 1996-629608, filed on 9 Apr 1996, now abandoned
PRAI US 1996-32263P 19961203 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Raymond, Richard L.
LREP Foley & Lardner
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 3269

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

TI **Calcilytic** compounds

AB The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

SUMM . . . Number WO 94/18959, and Nemeth et al., PCT/US94/12117, International Publication Number WO 95/11211, feature calcium receptor-active molecules and refer to **calcilytics** as compounds able to inhibit calcium receptor activity. For example, WO 94/18959 on page 8, lines 2-13 asserts:

SUMM . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca_{sup.2+} receptors. Such calcimimetics or **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . .

SUMM The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. The ability of a compound to "inhibit calcium receptor activity". . .

SUMM The use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient are described below. Also described below are techniques which can be used to obtain additional **calcilytic** compounds.

SUMM An example of featured **calcilytic** compounds are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives having the chemical formula: ##STR1##

SUMM Preferred **calcilytic** compounds have an IC_{sub.50}.ltoreq.50 .mu.M, more preferably an IC_{sub.50}.ltoreq.10 .mu.M, and even more preferably an IC_{sub.50}.ltoreq.1 .mu.M, as measured using. . .

SUMM Patients benefiting from the administration of a therapeutic amount of a **calcilytic** compound can be identified using standard techniques known to those in the medical profession. Diseases or disorders which can be. . .

SUMM Preferably, the **calcilytic** compounds are used to treat

diseases or disorders selected from the group consisting of: hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

SUMM . . . invention describes a method of treating a patient comprising the step of administering to the patient an amount of a **calcilytic** compound sufficient to increase serum PTH level. Preferably, the method is carried out by administering an amount of the compound. . .

SUMM Another aspect of the present invention features Structure I **calcilytic** compounds.

SUMM Another aspect of the present invention features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a **calcilytic** compound described herein. The pharmaceutical composition contains the **calcilytic** compound in a form suitable for administration into a mammal, preferably, a human being. Preferably, the pharmaceutical composition contains an amount of a **calcilytic** compound in a proper pharmaceutical dosage form sufficient to exert a therapeutic effect on a human being. However, multiple doses. . .

SUMM . . . or in vitro and is particularly useful to identify those Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives most able to act as **calcilytic** compounds. In vivo assays include measuring a physiological parameter related to calcium receptor activity, such as serum hormone levels or serum calcium ion concentration. In vitro assays include measuring the ability of the **calcilytic** compound to affect intracellular calcium concentration, or cellular hormone secretion. Examples of hormones levels which can be affected by **calcilytic** compounds include PTH and calcitonin.

SUMM The **calcilytic** compounds described herein can be used as part of in vivo or in vitro methods. Preferably, the compounds are used. . . a patient. Examples of in vitro uses, and other in vivo uses, include use in a method to identify other **calcilytic** compounds and use as a tool to investigate calcium receptor activity or the physiological effects of inhibiting calcium receptor activity. . .

SUMM The present application demonstrates the ability of **calcilytic** compounds to exert a physiologically relevant effect on a cell by illustrating the ability of such compounds to increase PTH secretion and also identifies a target site for **calcilytic** compounds. The present application is believed to be the first to demonstrate that **calcilytic** compounds can increase PTH secretion.

SUMM Calcium receptors are present on different cell types and can regulate different responses in different cell types. While the **calcilytic** compounds described herein are believed to act at a calcium receptor through a calcium receptor-activity modulating site, unless otherwise explicitly. . . or any particular mode of action. Rather, the present application demonstrates that compounds able to inhibit calcium receptor activity, whose **calcilytic** activity can be measured in vivo or in vitro, exert significant physiological effects. For example, the present application demonstrates the ability of different **calcilytic** compounds to prevent Ca.sup.2+ inhibition of PTH and, thereby, result in an increase in PTH release.

SUMM Preferred **calcilytic** compounds described herein are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. Other aspects of the present. . .

SUMM **Calcilytic** activity of a compound can be determined using techniques such as those described in the examples below and those described. . .

SUMM **Calcilytic** activity varies depending upon the cell type in which the activity is measured. For example, **calcilytic** compounds possess one or more, and preferably all, of the following

characteristics when tested on parathyroid cells in vitro:

SUMM . . . and cycloalk. Preferably, R.sub.1 is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl, optionally substituted longer-length alkyl, optionally substituted longer-length alkenyl or optionally substituted cycloalk.

SUMM More preferably, R.sub.1 is either an optionally substituted phenyl; an optionally substituted **naphthyl**; an optionally substituted pyridyl; an optionally substituted benzothiopyranyl; an optionally substituted carbazole; unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or monosubstituted. . .

SUMM . . . Preferably, R.sub.3 and R.sub.4 are each independently a lower alkyl, more preferably, R.sub.3 and R.sub.4 are each independently methyl or **ethyl**;

SUMM R.sub.5 is aryl. Preferably, R.sub.5 is either optionally substituted **naphthyl** or optionally substituted phenyl. More preferably, R.sub.5 is substituted phenyl having a substituent in the meta or para position and. . .

SUMM . . . substituted. Preferably, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl.

SUMM . . . an aryl, the aryl is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, or optionally substituted tetrahydronaphthyl. Preferred, R.sub.1 substituents are each independently selected from the group consisting of: unsubstituted alkyl, unsubstituted alkenyl,. . .

SUMM More preferred **calcilytic** compounds are Structure I derivatives where R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.6, Z, Y.sub.1, and Y.sub.2 are as described above for. . .

SUMM R.sub.5 is either phenyl substituted with one to four independently selected substituents or an optionally substituted **naphthyl** having up to four independently selected substituents. R.sub.5 substituents are provided in Section II, supra., including preferred embodiments. More preferably. . . in a meta or para position, more preferably, the substituent present in a meta or para position is either methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy.

SUMM The activity of different **calcilytic** compounds was measured using the Calcium Receptor Assay described below. Examples of compounds having an IC.sub.50.ltoreq.50 .mu.M include compounds 1,. . .

SUMM R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, or lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or. . .

SUMM R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, preferably the **naphthyl** is unsubstituted; or a substituted phenyl having one to four substituent with at least one substituent in a meta or para position selected from the group consisting of: methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, more preferably a methoxy is present in the para or meta position;. . .

SUMM The different **calcilytic** compounds described herein can have different stereochemistry around different groups. In an embodiment of

the present invention the Structure I. . .

SUMM The **calcilytic** compounds described herein can be formulated as a pharmaceutical composition to facilitate the administration of the compound to a patient. Preferred formulations contain a pharmaceutically acceptable carrier and a **calcilytic** compound as described in Section II, supra., including the different embodiments.

SUMM . . . effects to patients suffering from a variety of diseases or disorders. Diseases or disorders which can be treated using a **calcilytic** compound are known in the art and can be identified using the present application as a guide. For example, diseases. . .

SUMM Diseases and disorders which can be treated using the **calcilytic** compounds described herein include those due to different cellular defects related to calcium receptor activity in different cells, such as. . .

SUMM While **calcilytic** compounds of the present invention will typically be used to treat human patients, they may also be used to treat. . .

SUMM Preferably, **calcilytic** compounds are used in the treatment of bone and mineral-related diseases or disorders. Bone and mineral-related diseases or disorders comprise. . . and mineral-related diseases or disorders include osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**. More preferably, **calcilytic** compounds are used to treat **osteoporosis**, a disease characterized by reduced bone density and an increased susceptibility to fractures. **Osteoporosis** is associated with aging, especially in women.

SUMM One way of treating **osteoporosis** is by altering PTH secretion. PTH can have a catabolic or an anabolic effect on bone. Whether PTH causes a. . .

SUMM As demonstrated by the Examples provided below, **calcilytic** compounds stimulate secretion of PTH. Such **calcilytic** compounds can be used to increase bone formation in a patient, for example, by intermittent dosing, thus achieving intermittent increases. . .

SUMM The **calcilytic** compounds described by the present invention can be formulated for a variety of modes of administration, including systemic and topical. . .

SUMM The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50,. . .

DETD This example illustrates the use of the Calcium Receptor Inhibitor Assay. **Calcilytic** activity was measured by determining the IC.sub.50 of the test compound for blocking increases of intracellular Ca.sup.2+ elicited by extracellular. . .

DETD 7. To determine the Potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca.sup.2+ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca.sup.2+ elicited. . .

DETD Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives include compounds which have both **calcilytic** activity and .beta.-adrenergic receptor activity. If desired, .beta.-adrenergic activity can be reduced using appropriate functional groups and structural modifications. Modifications. . .

DETD In one embodiment of the present invention the **calcilytic**

compounds have an IC_{50} of 1.0 nM, at the β -adrenergic receptor as measured using the " β -Adrenergic Receptor Binding Assay" described below. In other embodiments, using the β -Adrenergic Receptor Assay **calcilytic** compounds have an IC_{50} of 1.0 μ M, and IC_{50} of 10.0 μ M.

DETD This example illustrates the ability of different **calcilytic** compounds to exert a biological effect on PTH secretion. PTH secretion was determined using dissociated bovine parathyroid cells as described.

DETD General Procedures for the Preparation of **Calcilytic** Compounds

DETD The **calcilytic** compounds described by the present invention can be prepared using standard techniques. For example, an overall strategy for preparing preferred.

DETD . . . many of the compounds was carried out as follows: A solution of glycidyl ether (i.e., 1,2-epoxy-3-phenoxypropane, 1 mmol) and excess **amine** (typically 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine, 1.5 mmol) in absolute ethanol (2 mL) is stirred overnight at 50-60.degree. C. The product is purified by.

DETD . . . washed with 10% aqueous $NaHCO_3$ (3.times.200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Kugelrohr distillation (about 100 microns) yielded 1-**naphthyl** glycidyl ether as a clear, colorless oil: GC/EI-MS, m/z (rel. int.) 200 (M^{sup.}+, 61), 184 (1), 169 (5), 157 (12), . . .

DETD A stirred solution of 1-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-fluorophenyl)ethylamine (334 mg, 2 mmol) in absolute ethanol (2 mL) was heated at.

DETD . . . mmol) were dissolved in 30 mL of water and enough acetone to maintain solubility at 0.degree. C. A solution of **ethyl** chloroformate (20.1 g, 185 mmol) in acetone (100 mL) was then added dropwise. An aqueous solution (95 mL) of sodium.

DETD Using the method of Example 5, supra, 1-**naphthyl** glycidyl ether (1.0 g, 5 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (1.0 mg, 5.6 mmol) were used to prepare the free base of.

DETD Preparation of N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine, Compound 28

DETD Resolution of the Enantiomers (R) and (S)-N-[2-Hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compounds 63 and 64

DETD The enantiomers (R) and (S)-N-[2-hydroxy-3-(2-**ethyl**)hexanoxypentyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine hydrochloride were prepared using the method of Example 7, supra, GC/EI-MS of each enantiomer gave m/z (rel. int.) 366 (M+1), . . . (21), 115 (11), 100 (4), 71 (21). The hydrochloride salt of each enantiomer was prepared by treatment of the free **amine** in diethyl ether with excess 1M HCl (diethyl ether). Evaporation of the solvent yielded the hydrochloride product as a solid.

DETD Preparation of N-[2-Hydroxy-3-(2-naphthoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl-amine** Hydrochloride, Compound 35

DETD Using the method of Example 4, supra, 2-**naphthyl** glycidyl ether (400 mg, 2 mmol) and 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (358 mg, 2 mmol) were used to prepare the free base of.

DETD Preparation of N-[2-Hydroxy-3-(1-adamantanoxypentyl)-1,1-dimethyl-2-(4-methoxyphenyl)**ethyl amine**, Compound 96

DETD Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1-**ethyl**-1-methyl-2-(4-methoxyphenyl)ethylamine Hydrochloride, Compound 113

DETD . . . washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by preparative TLC using **ethyl** acetate/hexane as the elutant. The yield of 1-**ethyl**-1-methyl-2-(4-hydroxyphenyl)nitroethane was 0.21 grams.

DETD . . . a suspension of 40% (wt/wt) potassium fluoride on alumina (0.73 g, 5 mmol) in 3 mL of acetonitrile were added 1-**ethyl**

-1-methyl-2-(4-hydroxyphenyl)nitroethane (0.21 g, 1.0 mmol) and iodomethane (0.21 g, 1.5 mmol). The reaction was stirred at room temperature for 4 days. . . washed with sodium bisulfite, sodium carbonate, and saturated brine, then dried over anhydrous sodium sulfate and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane was 0.183 g.

DETD . . . 5 mL of methanol, followed by the addition of sodium borohydride (0.05 g, 1.2 mmol). After stirring for 5 minutes, 1-ethyl-1-methyl-2-(4-methoxyphenyl)nitroethane (0.18 g, 0.807 mmol) in 3 mL of methanol was added, and stirred for 5 minutes. Sodium borohydride (0.11 g, . . . hydroxide. The ether layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated. The yield of 1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine was 0.127 grams.

DETD Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.086 g, 0.57 mmol) and 1-ethyl-1-methyl-2-(4-methoxyphenyl)ethylamine (0.11 g, 0.57 mmol) were used to prepare 90 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD Preparation of (R)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl Amine Hydrochloride, Compound 115

DETD Preparation of (S)-N-[2-Hydroxy-3-(2,3-dichlorophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl Amine Hydrochloride, Compound 116

DETD Preparation of N-(2-Hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(2-naphthyl)ethylamine Hydrochloride, Compound 120

DETD Using the method of Example 52, supra, 2-amino-methylnaphthalene (2.51 g, 16 mmol) was used to prepare 1.9 g of 1,1-dimethyl-2-(2-naphthyl)ethylamine.

DETD Using the method of Example 6, supra, 1,2-epoxy-3-phenoxypropane (0.163 g, 1.1 mmol) and 1,1-dimethyl-2-(2-naphthyl)ethylamine (0.26 g, 1.3 mmol) were used to prepare 243 mg of the title compound as a white solid: GC/EI-MS, m/z, . . .

DETD . . . 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine (230 mg, 1.5 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 130 mg of the title. . .

DETD . . . 1,1-di-methyl-2-(4-methoxyphenyl)ethylamine (180 mg, 1 mmol) were used to prepare the hydrochloride salt of the title compound. MPLC of the free amine (silica gel, 1% MeOH/CHCl₃), followed by treatment with an excess of 1 M HCl/ether, yielded 88 mg of a white. . .

DETD Synthesis of (R/S)-1-[[2,2-dimethyl-(4', methoxy)phenethyl]amino-2-hydroxy-4(1'-naphthyl)butane, Compound 162

DETD . . . with CH₂Cl₂ and was extracted with sodium sulfite (aqueous) and NaHCO₃ (aqueous), dried over MgSO₄, filtered and evaporated to give 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) that was carried without further purification.

DETD A solution of 1-[(2-oxoaryl)ethyl]-naphthalene (1 g) and 1,1-dimethyl-2(4-methoxyphenyl) ethylamine (985 mg, 5.5 mmol) in ethanol (25 mL) was heated at reflux for 12 hours: . . . addition of ether, crystals formed and were subsequently collected and dried in a vacuum oven to give 1.4 g of (R/S)-1-[[2,2-dimethyl-(4'methoxy)phenethyl]]amino-2-hydroxy-4(1'-naphthyl)-butane. ESMS [(M+H)⁺=378, .sup.1H NMR (CDCl₃, 360 MHz) @300.degree. K. .delta. 8.06 (1H, d of d), 7.83 (1H, d of d), . . .

DETD N-[12(g)-Hydroxy-3-[(2,3-dichloro-4-ditpropylsulfamoyl)phenoxy]-1-propyl]-N-(1-[1-dimethyl-2-(4-methoxyphenyl)ethyl]amine Hydrochloride Salt Compound 165

DETD e) N-[2(R)-Hydroxy-3-[(2,3-dichloro-4-dipropylsulfamoyl)phenoxy]-1-propyl]-N-[1,1-dimethyl-2-(4-methoxyphenyl)ethyl]amine

hydrochloride salt.

DETD Compound 92: N-(2-hydroxy-3-phenoxypropyl)-1,1-dimethyl-2-(1-naphthyl)ethylamine.

CLM What is claimed is:

- . . . OH and O-alkyl; R.sub.3 and R.sub.4 is each independently lower alk or together cyclopropyl; R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least. . .
- . . . OH, or O-alkyl; R.sub.3 and R.sub.4 is each independently lower alk or together cyclopropyl; R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least. . .
- . . . any of claims 2-4, wherein R.sub.2 is OH or methoxy, R.sub.6 is hydrogen, R.sub.3 and R.sub.4 are independently methyl or **ethyl**, and Z is O or S.
- . . . 8. The compound of claim 4, wherein R.sub.2 is hydrogen, R.sub.6 is hydrogen, R.sub.3 and R.sub.4 are independently methyl or **ethyl**; and Z is O.

10. The compound of claim 2, wherein said compound is N-(2(R)-Hydroxy-3-((2,3-dichloro-4-dipropylsulfamoyl)phenoxy)-1-propyl)-N-(1,1-dimethyl-2-(4-methoxyphenyl) **ethyl**) **amine** or a pharmaceutically acceptable salt or complex thereof.

11. A compound having the chemical formula: ##STR89## wherein R.sub.1 is **naphthyl** or phenyl; R.sub.2 is selected from the group consisting of: H, OH and O-alkyl; R.sub.3 and R.sub.4 is each independently lower alk or together cyclopropyl; R.sub.5 is either an optionally substituted **naphthyl** having one to four substituents independently selected from the group consisting of: methyl, **ethyl**, isopropyl, methoxy, Cl, F, Br, and lower haloalkoxy, or a substituted phenyl having one to four substituents with at least. . .

L2 ANSWER 6 OF 26 USPTAFULL on STN

AN 2003:24359 USPTAFULL

TI **Calcilytic** compounds

IN Largo, Maria Amparo, Audubon, PA, UNITED STATES

Callahan, James Francis, Philadelphia, PA, UNITED STATES

Bhatnagar, Pradip Kumar, Exton, PA, UNITED STATES

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PI US 2003018203 A1 20030123

AI US 2002-181338 A1 20020717 (10)

WO 2001-US2402 20010124

DT Utility

FS APPLICATION

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CLMN Number of Claims: 14

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1350

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel **calcilytic** compounds and methods of using them are provided.

TI **Calcilytic** compounds

AB Novel **calcilytic** compounds and methods of using them are provided.

SUMM [0001] The present invention relates to novel **calcilytic** compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.

SUMM [0006] Various compounds are known to mimic the effects of extra-cellular Ca.sup.2+ on a calcium receptor molecule. **Calcilytics** are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca.sup.2+. **Calcilytics** are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators, which are active at Ca.sup.2+ receptors. Such **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . . secretion of which is regulated or affected by activity at one or more Ca.sup.2+ receptors. Target diseases or disorders for **calcilytic** compounds include diseases involving abnormal bone and mineral homeostasis.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM . . . hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and **osteoporosis**.

SUMM . . . systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and **naphthyl**. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halogen, C.sub.1-4 alkyl, OCF.sub.3, CF.sub.3, OMe, . . .

SUMM . . . Heteroaryl includes carbocyclic heteroaryl, aryl-heteroaryl and biheteroaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and **naphthyl**. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halogen, C.sub.1-4 alkyl, OCF.sub.3, CF.sub.3, OMe, . . .

SUMM [0051] 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester;

SUMM [0053] 3-(4-Cyano-3-[(S)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester;

SUMM [0056] 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-methoxy-**ethyl** ester;

SUMM [0060] 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-ethoxy **ethyl** ester;

SUMM [0062] 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 1-**ethyl**-propyl ester;

SUMM [0064] 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-methoxy-1-methyl-**ethyl** ester;

SUMM [0070] 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;

SUMM [0072] 3-(3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;

SUMM [0074] 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionate **ethyl** ester;

SUMM [0075] 3-(2-Chloro-4-cyano-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester;

SUMM [0077] 3-(2-Fluoro-4-cyano-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester;

SUMM [0079] 3-(2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;

SUMM [0080] 4-(2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0083] 4-(4-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0085] 4-(3-Cyano-4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0087] 3-(2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;

SUMM [0088] 4-(2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0091] 4-(4-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0093] 4-(3-Cyano-4-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;

SUMM [0095] (S)-2-Amino-3-[4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-3-nitro-phenyl]-propionic acid **ethyl** ester;

SUMM [0097] (R)-2-Amino-5-[4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-pentanoic acid **ethyl** ester;

SUMM [0099] 5-[4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-pentanoic acid **ethyl** ester;

SUMM [0101] (R)-2-Amino-5-[4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionic acid **ethyl** ester;

SUMM [0103] (S)-2-Amino-5-[4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionic acid **ethyl** ester; and

SUMM [0107] 3-[4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionic **ethyl** ester;

SUMM [0110] 3-[4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionic acid 2-ethoxy **ethyl** ester;

SUMM [0111] 3-[4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl]-propionic acid 2-methoxy-1-methyl-**ethyl** ester;

SUMM [0113] 3-[4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl]-propionic acid **ethyl** ester;

SUMM [0115] 3-[3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl]-propionic acid **ethyl** ester;

SUMM [0117] 3-[4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionate **ethyl** ester

SUMM [0120] 3-[4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl]-propionic **ethyl** ester; and

SUMM . . . described in Schemes 1-3. In general, a solution of a glycidyl ether (e.g., 7 of Scheme 1) and a primary **amine** (e.g., 2-indan-2-yl-1,1-dimethyl-ethylamine of Scheme 1) in a solvent such as absolute ethanol, acetonitrile, toluene, THF or any other similar solvent. . .

SUMM [0132] The **calcilytic** compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic. . .

SUMM [0136] The amounts of various **calcilytic** compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC.sub.50, EC.sub.50, . . .

SUMM . . . helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and **osteoporosis**.

SUMM [0157] **Calcilytic** activity was measured by determining the IC₅₀ of the test compound for blocking increases of intracellular Ca²⁺ elicited by extracellular . . .

SUMM [0167] 7. To determine the potential **calcilytic** activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca²⁺ from 1 to 2 mM. **Calcilytic** compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca²⁺ elicited. . .

SUMM [0171] A typical reaction mixture contains 2 nM ³H compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-naphthyl)ethylamine), or ³H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume. . .

DETD . . . mol). The mixture was stirred at RT for 16 h, concentrated in vacuo, and the oily residue was dissolved in **ethyl** acetate, washed with 2.5 N sodium hydroxide, water, and brine, dried (MgSO₄), and concentrated in vacuo to give the title. . .

DETD [0178] c) N-(2-Indan-2-yl-1,1-dimethyl-**ethyl**)-acetamide

DETD . . . added. The mixture was allowed to warm to RT, stirred for 16 h, poured into ice water, and extracted with **ethyl** acetate. The combined organic extract was washed with 2.5 N sodium hydroxide, water, and brine, dried (MgSO₄), and concentrated in vacuo to give an oily residue that was triturated with hexane and a few drops of **ethyl** acetate, seeded, and cooled to afford a solid which was isolated by filtration to afford the title compound as tan. . .

DETD . . . (13 g), stirred, and heated to 190.degree. C. for 24 h. The mixture was poured into water and extracted with **ethyl** acetate. The combined organic phase was washed with brine and extracted with 1 N hydrochloric acid. The combined acidic extract was washed with **ethyl** acetate, basified with 2.5 N sodium hydroxide, and extracted with **ethyl** acetate. The combined organic extract was washed with brine, dried (MgSO₄), and concentrated in vacuo to afford the title compound. . .

DETD Preparation of **ethyl** (R)-4-cyano-3-(oxiranylmethoxy)benzenepropionate

DETD [0182] a) **Ethyl** 3-hydroxybenzenepropionate

DETD . . . and concentrated in vacuo to about 50 mL. Water (.about.200 mL) was added and the mixture was extracted three-times with **ethyl** acetate. The combined **ethyl** acetate extract was washed with water and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the title compound. . .

DETD [0184] b) **Ethyl** 4-formyl-3-hydroxybenzenepropionate

DETD . . . h. The reaction was cooled, 6 N hydrochloric acid (400 mL) was added and the resulting mixture was extracted with **ethyl** acetate. The combined **ethyl** acetate extract was washed with water, dried (MgSO₄), filtered and concentrated in vacuo. The residual oil was purified by flash column chromatography (silica gel, 10% **ethyl** acetate/hexane) to give the title compound (66.6 g, 75%).

DETD [0186] c) **Ethyl** 3-hydroxy-4-[(hydroxyimino)methyl]benzenepropionate

DETD . . . reaction was stirred under argon at reflux for 18 h, concentrated in vacuo, and the residual oil was dissolved in **ethyl** acetate and washed with 1N hydrochloric acid. The **ethyl** acetate phase was dried (MgSO₄), filtered, and

concentrated in vacuo to give the title compound as an oil which was. .

- DETD [0188] d) **Ethyl** 3-acetoxy-4-cyanobenzenepropionate
DETD . . . and refluxed under argon for 90 min. The reaction was concentrated in vacuo and the resulting oil was dissolved in **ethyl** acetate and washed with water. The **ethyl** acetate layer was dried (MgSO.sub.4), filtered, and concentrated in vacuo to give the title compound as an oil which was. . .
- DETD [0190] e) **Ethyl** 4-cyano-3-hydroxybenzenepropionate
DETD . . . was neutralized with 6 N hydrochloric acid to pH 5 and concentrated in vacuo. The resulting mixture was extracted with **ethyl** acetate. The **ethyl** acetate solution was dried (MgSO.sub.4), filtered, and concentrated in vacuo to give the title compound as an oil [61.9 g, . . .
- DETD [0192] f) **Ethyl** (R)-4-cyano-3-(oxiranylmethoxy)benzenepropionate
DETD . . . cooled, filtered, and the filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica, 30% **ethyl** acetate/hexane) to yield the title compound (29.5 g, 82.4%).
- DETD Preparation of **Ethyl** 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionate
DETD . . . at 70.degree. C. under argon for 20 h. The reaction was cooled, concentrated and the residue partitioned between water and **ethyl** acetate. The organic layer was washed with 10% Na.sub.2CO.sub.3 (aqueous), brine, dried over MgSO.sub.4 and evaporated. Purification by flash chromatography. . .
- DETD Preparation of 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid 2-methoxy-**ethyl** ester hydrochloride salt
DETD [0201] A solution of 3-(4-Cyano-3-hydroxy-phenyl)-propionic acid **ethyl** ester (2.2 g, 10 mmol) in ethanol (10 mL) and water (40 mL) was treated with aqueous sodium hydroxide solution. . .
- DETD Preparation of 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid 2-ethoxy **ethyl** ester trifluoroacetate salt
DETD Preparation of 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid 2-methoxy **ethyl** ester trifluoroacetate salt
DETD Preparation of 3-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid 1-**ethyl**-propyl ester trifluoroacetate salt
DETD Preparation of 3-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid 2-methoxy-1-methyl-**ethyl** ester
DETD [0226] b) 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy)-phenyl)-propionic acid **ethyl** ester.
DETD [0227] Following the procedure described in Example 3 except using **amine** from Example 21 (a), the above titled compound was obtained. MS(ES) m/z 479.6 (M+H).sup.+; Elemental analysis: theoretical for C.sub.29H.sub.38N.sub.2O.sub.4.HCl.1/2H.sub.2O: C, . . .
- DETD [0230] Following the procedure described in Example 3 using **ethyl** (R)-2-cyano-4-(oxiranylmethoxy)benzenepropionate and the **amine** from example 21(a) the above titled compound was obtained. MS(ES) m/z 451.4 (M+H).sup.+.
- DETD . . . RT overnight. The reaction was filtered, the filtrate was concentrated in vacuo and the residue purified by flash column chromatography (**ethyl** acetate/hexane, 1:99) to yield the above titled compound as a pale yellow oil (1.7 g, 67%).
- DETD [0233] b) N-(2-Indan-5-yl-1,1-dimethyl-**ethyl**)-acetamide
DETD . . . procedure described in Example 1 (c) the above titled compound

was obtained as a crystalline solid. Melting point 130-131.degree. C. (ethyl acetate); MS(ES) m/z 463.7 (2M+H).sup.+, 322.7 (M+H).sup.+; Elemental Analysis: theoretical for C.sub.15H.sub.21NO: C, 77.85; H, 9.15; N, 6.05. Found: C, . . .

DETD [0237] d) **Ethyl** 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionate hydrochloride salt.

DETD [0238] Following the procedure described in Example 3 using the amine from Example 23 (c) the above titled compound was obtained. MS(ES) m/z 465.8 (M+H).sup.+; Elemental analysis: theoretical for C.sub.28H.sub.36N.sub.2O.sub.4.HCl.(fraction (3/4))H.sub.2O:. . .

CLM What is claimed is:

4. A compound according to claim 1 selected from the group consisting of: 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; 3-(4-Cyano-3-[(S)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester; 3-(4-Cyano-3-[(S)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid octyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-methoxy-**ethyl** ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid butyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid isopropyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid pentyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-ethoxy **ethyl** ester; 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 3-methyl-butyl ester; 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 1-**ethyl**-propyl ester; 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid sec-butyl ester; 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-methoxy-1-methyl-**ethyl** ester; 2,2-Dimethyl-propionic acid 3-(4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propanoyloxymethyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid (S)-2-amino-3-methyl-butyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 5-amino-pentyl ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid methyl ester; 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid; 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester; 3-(3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid; 3-(3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionate **ethyl** ester; 3-(2-Chloro-4-cyano-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester; 3-(2-Chloro-4-cyano-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; 3-(2-Fluoro-4-cyano-5-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester; 3-(2-Fluoro-4-cyano-5-[(R)-2-hydroxy-3-

(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid;
 3-{2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;
 4-{2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;
 3-{2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid; 4-{2-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 4-{4-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;
 4-{4-Cyano-3-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 4-{3-Cyano-4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;
 4-{3-Cyano-4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 3-{2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid **ethyl** ester;
 4-{2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;
 3-{2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-propionic acid;
 4-{2-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 4-{4-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid **ethyl** ester;
 4-{4-Cyano-3-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 4-{3-Cyano-4-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 4-{3-Cyano-4-[(R)-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-phenyl)-butyric acid;
 (S)-2-Amino-3-{4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-3-nitro-phenyl)-propionic acid **ethyl** ester;
 (S)-2-Amino-3-{4-[(R)-3-(1,1-dimethyl-2-naphthalen-2-yl-ethylamino)-2-hydroxy-propoxy]-3-nitro-phenyl)-propionic acid; (R)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-pentanoic acid **ethyl** ester;
 (R)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-pentanoic acid;
 5-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-pentanoic acid **ethyl** ester;
 5-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-pentanoic acid;
 (R)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid **ethyl** ester;
 (R)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid;
 (S)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid **ethyl** ester;
 and (S)-2-Amino-5-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; and pharmaceutically acceptable salts thereof.

5. A compound according to claim 4 selected from the group consisting of:
 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester;
 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid;
 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid isopropyl ester;
 3-{4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-ethoxy **ethyl** ester;
 3-{4-cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid 2-methoxy-1-methyl-**ethyl** ester;
 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy]-phenyl)-propionic acid;
 3-(4-Cyano-3-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-

ethylamino]-2-hydroxy-propoxy)-phenyl)-propionic acid **ethyl** ester; 3-(3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy)-phenyl)-propionic acid; 3-(3-Cyano-4-[(R)-3-[1,1-dimethyl-2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-2-hydroxy-propoxy)-phenyl)-propionic acid **ethyl** ester; 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; and 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-5-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionate **ethyl** ester; and pharmaceutically acceptable salts and complexes thereof.

6. A compound according to claim 5 selected from the group consisting of: 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic **ethyl** ester; and 3-(4-Cyano-3-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl)-propionic acid; and pharmaceutically acceptable salts and complexes thereof.

. . . selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia, malignancy and **osteoporosis**.

10. A method according to claim 8 wherein the bone or mineral disease or disorder is **osteoporosis**.

12. A method according to claim 7 wherein the **calcilytic** compound is co-administered with an anti-resorptive agent.

14. A compound selected from the group consisting of:
2-Indan-2-yl-1,1-dimethyl-ethylamine; Indan-2-yl-acetic acid methyl ester; 1-Indan-2-yl-2-methyl-propan-2-ol; N-(2-Indan-2-yl-1,1-dimethyl-**ethyl**)-acetamide; **Ethyl** (R)-4-cyano-3-(oxiranylmethoxy)benzenepropionate; **Ethyl** 4-formyl-3-hydroxybenzenepropionate; **Ethyl** 3-hydroxy-4-[(hydroxyimino)methyl]benzenepropionate; **Ethyl** 3-acetoxy-4-cyanobenzenepropionate; and **Ethyl** 4-cyano-3-hydroxybenzenepropionate.

L2 ANSWER 7 OF 26 USPATFULL on STN

AN 2002:201853 USPATFULL

TI **Calcilytic** compounds

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DT Utility

FS GRANTED

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CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention features **calcilytic** compounds. "**calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

TI **Calcilytic** compounds

AB The present invention features **calcilytic** compounds. "**calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. Also described are the use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient; and techniques which can be used to obtain additional **calcilytic** compounds.

SUMM . . . Number WO 94/18959, and Nemeth et al., PCT/US94/12117, International Publication Number WO 95/11211, feature calcium receptor-active molecules and refer to **calcilytics** as compounds able to inhibit calcium receptor activity. For example, WO 94/18959 on page 8, lines 2-13 asserts:

SUMM . . . can be identified and used as lead molecules in the discovery, development, design, modification and/or construction of useful calcimimetics or **calcilytics** which are active at Ca_{sup.2+} receptors. Such calcimimetics or **calcilytics** are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides. . .

SUMM The present invention features **calcilytic** compounds. "**Calcilytic** compounds" refer to compounds able to inhibit calcium receptor activity. The ability of a compound to "inhibit calcium receptor activity". . .

SUMM The use of **calcilytic** compounds to inhibit calcium receptor activity and/or achieve a beneficial effect in a patient are described below. Also described below are techniques which can be used to obtain additional **calcilytic** compounds.

SUMM An example of featured **calcilytic** compounds are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives having the chemical formula: ##STR1##

SUMM Preferred **calcilytic** compounds have an IC_{sub.50} of 10⁻⁵ to 10⁻⁹ M, more preferably an IC_{sub.50} of 10⁻⁶ to 10⁻⁸ M, and even more preferably an IC_{sub.50} of 10⁻⁷ to 10⁻⁷ M, as measured using. . .

SUMM Patients benefiting from the administration of a therapeutic amount of a **calcilytic** compound can be identified using standard techniques known to those in the medical profession. Diseases or disorders which can be. . .

SUMM Preferably, the **calcilytic** compounds are used to treat diseases or disorders selected from the group consisting of: hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and **osteoporosis**.

SUMM . . . invention describes a method of treating a patient comprising the step of administering to the patient an amount of a **calcilytic** compound sufficient to increase serum PTH level. Preferably, the method is carried out by administering an amount of the compound. . .

SUMM Another aspect of the present invention features Structure I **calcilytic** compounds.

SUMM Another aspect of the present invention features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a

calcilytic compound described herein. The pharmaceutical composition contains the **calcilytic** compound in a form suitable for administration into a mammal, preferably, a human being. Preferably, the pharmaceutical composition contains an amount of a **calcilytic** compound in a proper pharmaceutical dosage form sufficient to exert a therapeutic effect on a human being. However, multiple doses. . . .

SUMM . . . or in vitro and is particularly useful to identify those Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives most able to act as **calcilytic** compounds. In vivo assays include measuring a physiological parameter related to calcium receptor activity, such as serum hormone levels or serum calcium ion concentration. In vitro assays include measuring the ability of the **calcilytic** compound to affect intracellular calcium concentration, or cellular hormone secretion. Examples of hormones levels which can be affected by **calcilytic** compounds include PTH and calcitonin.

SUMM The **calcilytic** compounds described herein can be used as part of in vivo or in vitro methods. Preferably, the compounds are used. . . a patient. Examples of in vitro uses, and other in vivo uses, include use in a method to identify other **calcilytic** compounds and use as a tool to investigate calcium receptor activity or the physiological effects of inhibiting calcium receptor activity. . . .

DETD The present application demonstrates the ability of **calcilytic** compounds to exert a physiologically relevant effect on a cell by illustrating the ability of such compounds to increase PTH secretion and also identifies a target site for **calcilytic** compounds. The present application is believed to be the first to demonstrate that **calcilytic** compounds can increase PTH secretion.

DETD Calcium receptors are present on different cell types and can regulate different responses in different cell types. While the **calcilytic** compounds described herein are believed to act at a calcium receptor through a calcium receptor-activity modulating site, unless otherwise explicitly. . . or any particular mode of action. Rather, the present application demonstrates that compounds able to inhibit calcium receptor activity, whose **calcilytic** activity can be measured in vivo or in vitro, exert significant physiological effects. For example, the present application demonstrates the ability of different **calcilytic** compounds to prevent Ca.sup.2+ inhibition of PTH and, thereby, result in an increase in PTH release.

DETD Preferred **calcilytic** compounds described herein are Structure I .alpha.,.alpha.-disubstituted arylalkylamine derivatives able to inhibit calcium receptor activity. Other aspects of the present. . . .

DETD **Calcilytic** activity of a compound can be determined using techniques such as those described in the examples below and those described. . . .

DETD **Calcilytic** activity varies depending upon the cell type in which the activity is measured. For example, **calcilytic** compounds possess one or more, and preferably all, of the following characteristics when tested on parathyroid cells in vitro:

DETD . . . and cycloalk. Preferably, R.sub.1 is either optionally substituted phenyl, optionally substituted pyridyl, optionally substituted benzothiopyranyl, optionally substituted carbazole, optionally substituted **naphthyl**, optionally substituted tetrahydronaphthyl, optionally substituted longer-length alkyl, optionally substituted longer-length alkenyl or optionally substituted cycloalk.

DETD More preferably, R.sub.1 is either an optionally substituted phenyl; an optionally substituted **naphthyl**; an optionally substituted pyridyl; an optionally substituted benzothiopyranyl; an optionally substituted carbazole; unsubstituted longer-length alkyl; unsubstituted longer-length alkenyl; or monosubstituted. . . .